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WATER INTOXICATION *

LEONARD G. ROWNTREE, M.D.
ROCHESTER, MINN.

Strange as it may appear, little or nothing is known concerning the effects of an excessive intake of water. Statements such as "even water must be toxic" are heard almost daily, yet the toxicity attending excessive ingestion of water has been taken for granted rather than proved. So far as I am aware the symptoms of water poisoning and the mode of death in water intoxication have never been determined. This is due, in part, to the fact that quantities in excess of those taken voluntarily are necessary for its production, and that the rôle of water intoxication in pathologic conditions has not as yet been fully appreciated.

Nature has provided adequately against water intoxication. The sensation of satiety following the ingestion of small or moderate quantities of water renders the subsequent ingestion of larger amounts increasingly difficult. The pylorus prevents the sudden or immediate egress of large volumes of water, and consequently excessive ingestion results in gastric distention, which is followed in man, and in certain animals, by regurgitation and vomiting. In some animals diarrhea results. Water is an extremely effective diuretic. Absorption of large quantities promptly induces diuresis which prevents accumulation in the body. Thus, the factor of safety is great.

THE TOXICITY OF WATER FOR LOWER ORDERS

The toxicity of pure, fresh and distilled water for the lower orders of life, especially for fish, for isolated organs, for unicellular organisms and for certain cells, has been the subject of many investigations since the time of Paul Bert,[1] who, in 1866, ascribed the toxic effect of fresh water for the mullet to the difference in osmotic pressure between fresh water and sea water, causing the tissues to absorb water in excess. Plateau,[2] in 1871, ascribed the toxic effect of fresh water for marine crustaceans to the diffusion of salts from the organism, an explanation

* From the Division of Medicine, The Mayo Foundation.

* The word "intoxication" as used here designates poisoning and has no reference to alcohol intoxication.

1. Bert, P.: Note sur la mort des poissons de mer dans l'eau douce, Mém. de la soc. d. sc. phys. et Naturelles d. Bord., **4**:47-49, 1866.

2. Plateau, F.: Recherches physico-chimiques sur les articules aquatiques, Mem. d. l'acad. Roy. d. Belgique **36**:, 1870. Quoted by Bullot.

given by J. Loeb [3] for the same phenomena which he observed in his studies on a marine gammarus.

The toxicity of distilled and of fresh water for lower species was a topic of lively discussion toward the close of the last century. Ringer and his collaborators,[4] in a series of papers published from 1883 to 1894, held that distilled water was strikingly toxic for the goldfish, the minnow, the sticklebock, the eel, the newt, the tadpole, the egg of the frog and for a fresh water worm, *Tubifex rivulorum*. He demonstrated that distilled water caused the disappearance of ciliary motion in less than twenty-four hours in the vibratile epithelium of the gills of the anadon. He ascribed toxicity of distilled water to: (1) subtraction from the organism of salts essential to life; (2) penetration of water into cells according to the laws of osmosis, and (3) imbibition of water by intercellular substances. But in 1893, there appeared a posthumous publication of a paper written by Naegeli [5] in which he proved that in his series of experiments traces of copper in the water were the sole cause of death for the fresh water alga, Spirogyra. These traces were carried over from the still during distillation. It was found that copper in dilution of 1:77,000,000 sufficed to kill. Locke,[6] in 1895, repeated some of these studies and showed that water distilled from and kept in glass is innocuous for tadpoles and *Tubifex rivulorum*. Ringer,[7] in 1897, confirmed these findings. The lack of toxicity of distilled water for the paramecium was demonstrated by Jennings [8] in 1897; for the young trout and tadpole by Moore [9] in 1900, and for a fresh water planarian, *Planaria maculata*, by Lillie [10] in 1900.

On the other hand, the toxicity of distilled water for the fresh water gammarus has been definitely proved by Loeb and by Bullot,[11] the

3. Loeb, J.: Ueber die relative Giftigkeit von Destillirtem Wasser, Zuckerlösungen und Lösungen von einzelnen Bestandtheilen des Seewassers für Seethiere, Arch. f. Physiol. **97**:394-409, 1903.

4. Ringer, S., and Phear, A. G.: The Influence of Saline Media on the Tadpole, J. Physiol. **17**:423-432, 1894.

5. Nägeli, C.: Ueber oligodynamische Ersheinungen in lebenden Zellen, mit einem Vorwort von S. Schwendener und einem Nachtag von C. Cramer, Denkschriften d. Schweiz. Naturforsch. Gesellsch **33**:, 1893. Quoted by Locke.

6. Locke, F. S.: On a Supposed Action of Distilled Water as Such on Certain Animal Organisms, J. Physiol. **18**:319-331, 1895.

7. Ringer, S.: The Action of Distilled Water on Tubifex, Proc. Phys. Soc., J. Physiol. **22**:14-15, 1897.

8. Jennings, H. S.: Studies on Reactions to Stimuli in Unicellular Organisms. I. Reactions on Chemical, Osmotic and Mechanical Stimuli in the Ciliate Infusoria, J. Physiol. **21**:258-322, 1897.

9. Moore, A.: Further Evidence of the Poisonous Effects of a Pure Sodium Chlorid Solution, Am. J. Physiol. **4**:386-396, 1900.

10. Lillie, F. R.: Some Notes on Regeneration and Regulation in Planarians, Am. Naturalist **34**:, 1900. Quoted by Bullot.

11. Bullot, G.: On the Toxicity of Distilled Water for the Fresh Water Gammarus. Suppression of This Toxicity by the Addition of Small Quantities of Sodium Chlorid, California University Publication, Physiology **1**:198-217, 1904.

latter ascribing the toxicity encountered to the properties of distilled water itself. He also found that the addition of sodium chlorid suppressed this toxicity. Sufficient sodium chlorid to yield 8:100,000 molecular salt solution sufficed to overcome the toxic properties of distilled water.

TOXICITY RESULTING IN MAN FROM EXCESSIVE INGESTION OF WATER [12]

Excessive ingestion of water is rarely encountered clinically in health or in disease, except, perhaps, in certain febrile diseases and in diabetes insipidus. In health, possibly, the largest amounts have been ingested in experiments concerned in investigations of the physiology of diuresis. Thus, in the experiments of MacCallum and Benson [13] as much as 2,500 c.c. was ingested in the course of two hours and the output of urine reached 20 c.c. each minute. Priestley [14] drank two liters of water within fifteen minutes. In one experiment he took 5,500 c.c. of fluid within six hours. During the same period he passed 5,460 c.c. of urine. Diuresis reached the rate of 1,200 c.c. each hour with a total output for a single hour of 888 c.c. Amberg and Austin,[15] in the study of skin elasticity, imbibed three liters of water within twenty minutes. Amberg says that elastometric measurements could not be made because of the development of tremor and muscle twitching.

In typhoid fever large quantities of water, five, six or even from eight to twelve liters each day, have been and are still used at times without the appearance of untoward symptoms. Miller and Williams,[16] on administering water up to ten liters each day to patients suffering from chronic nephritis and hypertension, noted marked increase of blood pressure, headache, dizziness, restlessness, chills, fulness of the abdomen, vomiting, dyspnea, cramps in the legs, and marked increase in weight. These results are in striking contrast with the entire absence

12. Pure water, as distinguished from distilled water, has been studied by Kohlrausch and Heydweiller. From the standpoint of electrical conductivity, water purer than distilled water may be obtained from freshly melted ice from glaciers in high mountains. According to Hans Koeppe (Reines Wasser; seine Giftwirkung und sein Vorkommen in der Natur, Deutsch. med. Wchnschr. **24**: 624-626, 1898), such pure water does not slake the thirst and is inherently toxic, leading to vomiting and gastric catarrh. However, he furnishes no details relative to this toxicity.

13. MacCallum, A. B., and Benson, C. C.: On the Composition of Dilute Renal Excretions, J. Biol. Chem. **6**:87-104, 1909.

14. Priestley, J. G.: The Regulation of Excretion of Water by the Kidneys, J. Physiol. **1**:304-311, 1916.

15. Amberg, S., and Austin, R. S.: Personal communication.

16. Miller, J. L., and Williams, J. L.: The Effect on Blood Pressure and the Nonprotein Nitrogen in the Blood of Excessive Fluid Intake, Am. J. M. Sc. **161**:327-334, 1921.

of symptoms in patients with diabetes insipidus who ingest similar amounts. In this disease, the rate of water exchange is high, not infrequently at a higher level than from 10 to 12 liters each day, and it may be maintained at this level for months or years without the appearance of untoward symptoms, such are are seen in water intoxication. In Trousseau's [17] case, the highest rate of water exchange on record, the urinary output was 43 liters each day, and the water intake 40 liters. With the water balance set at this almost unbelievable level, no signs of water intoxication developed, probably because of the prompt elimination of water. In all probability it is not the quantity of water ingested or the rate of water exchange, but rather an intake in excess of the ability of the body to excrete; that is, a positive balance with water accumulation in the body, which is responsible for the development of water intoxication. On the other hand, it may be due to the excess of water robbing the body of salt.

WATER INTOXICATION SUBSEQUENT TO THE ADMINISTRATION OF PITUITARY EXTRACT

Recently Larson, Weir and Rowntree [18] called attention to the peculiar form of intoxication resulting from the excessive intake of water subsequent to subcutaneous administration of pituitary extract. Three patients with diabetes insipidus, after receiving pituitary extract subcutaneously, continued to take water in the amounts to which they had become accustomed, that is, at the rate of from 8 to 10 liters each day. Within a few hours, headache, nausea, asthenia, incoordination and staggering gait developed and in one instance slight subcutaneous edema. The toxic manifestations were extremely severe and in one instance became alarming and occasioned grave concern to those in attendance.

Owing to the severity of the reaction in man, experiments were carried out solely on animals. Water intoxication was readily induced in dogs through excessive ingestion of water subsequent to the subcutaneous administration of pituitary extract. The symptoms of poisoning were asthenia, restlessness, frequency of urination, diarrhea, salivation, nausea, retching, vomiting, tremor, muscle twitching, ataxia, convulsions, frothing at the mouth, stupor and coma, ending in death in a large proportion of the animals. In reporting this work, the authors asserted that this intoxication could not be induced by pituitary extract alone or by water alone, but only by the combination of the two.

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17. Trousseau, A.: Lectures on Clinical Medicine, London, Hardwicke, 1857.

18. Larson, E. E., Rowntree, L. G., and Weir, J. F.: Studies in Diabetes Insipidus, Water Balance, and Water Intoxication, Arch. Int. Med. **29**:306-330 (March) 1922.

THE EXPERIMENTAL INDUCTION OF ACUTE WATER INTOXICATION IN MAMMALIANS

Considering it likely that water was responsible for the intoxication and that pituitary extract favored its development through lessening the rate of excretion and lowering the rate of water exchange, or through rendering easier its escape from the vascular system into the tissues, I continued the research. In this series of experiments water was administered at a more rapid rate, that is, 50 c.c. of water for each kilogram of body weight every half hour instead of every hour, as in the earlier experiments. This amount insures an intake of water greater than the capacity of the organism to excrete it. The adoption of this simple modification in technic has proved very efficacious and has regularly resulted in the development of the manifestations of water intoxication. Tap water [19] or distilled water (from blocked tin or glass), irrespective of its temperature, has proved equally toxic. Water intoxication has been produced in dogs, cats, rabbits and guinea-pigs.

Water was administered readily to all of these animals through the use of an appropriately sized stomach tube and the mouth gag. For guinea-pigs, the ureteral catheter answered admirably. The handling of cats and rabbits is simplified through the use of the box method employed by Keyser.[20] Prior to the administration of water, the weight and temperature of the animals were taken. This was repeated at the onset of convulsions and again at the close of the experiment. In all experiments, water was administered at intervals of one-half hour. In the interim the animals were removed from the box, placed in a cage or on the floor and kept under careful observation. Subsequent to the development of convulsions they were returned to their cages, except when death seemed imminent, under which conditions observations were continuous. A necropsy was performed as soon after death as possible.

THE MANIFESTATIONS OF WATER INTOXICATION IN VARIOUS ANIMALS

Reference has been made to the character of the symptoms of water intoxication encountered in animals subsequent to the administration of pituitary extract. Generally speaking, the clinical picture is much the same whether or not pituitary extract is used. However, in animals

19. An analysis was made March 4, 1920, by the Minnesota State Board of Health of the water supply of Rochester, Minn. The report states: "The field survey shows conditions which are satisfactory from a sanitary point of view, and in the analytical results indications of contamination were not found. The water from this supply can be considered safe for public consumption."

20. Keyser, L. D.: A Box for Handling Small Animals in the Laboratory, J. Lab. & Clin. M. 7:761-762, 1922.

under the influence of pituitary extract, irritability of the bladder and bowels is more common, as evidenced by more frequent and more ineffectual attempts at urination and defecation. Some form of nervous and mental excitation also develops, as evidenced by restlessness, aimless activity and constant running about. Under the influence of pituitary extract, coma is apparently somewhat deeper and convulsions are more pronounced, although this is difficult to prove.

In dogs, the symptoms of water intoxication consist of asthenia, restlessness, frequency of urination, nausea, retching, vomiting, salivation, muscle twitching, ataxia, tonic and clonic convulsions associated with frothing at the mouth and stupor or coma, ending in death or complete recovery within a few hours. Early in the intoxication, the

TABLE 1.—WATER INTOXICATION IN A DOG (F10)

	Time	Weight, Kg.	Water Intake, C.c.	Temperature, C.	Remarks
A	9:10 a.m.	5.5	250	37.5	Lively and vivacious
	9:40 a.m.	...	250		
	10:20 a.m.	...	250		
	10:40 a.m.	...	250	....	Diarrhea, vomiting, quiet and depressed, and ataxic on walking
	11:10 a.m.	...	250		
	11:40 a.m.	...	250		
	12:30 p.m.	...	250	....	Salivated, vomiting, convulsions, followed by stupor, weakness, flaccidity, abject helplessness
	1:45 p.m.	6.0			
B	1:50 p.m.	...	...	...	55 c.c. 10 per cent. sodium chlorid solution; stool immediately after injection; shook himself and lay down quietly
	2:00 p.m.				
	3:00 p.m.	..	...	38.0	Walks; markedly improved, salivation disappeared; voids profusely
	5:00 p.m.	5.6	...	....	Apparently normal

animals often attempt to hide in a corner; later they lie down and become apprehensive and watchful. As a rule, the convulsions resemble those of strychnin in their severity and may recur repeatedly at intervals of a few minutes. In the period between convulsions, a state of extreme asthenia, stupor or coma supervenes. Although deep coma is encountered at times, more often the eyes are open and the animal is in a state of profound asthenia and abject helplessness, accompanied by complete flaccidity. The animal may lie on its side, or occasionally on its abdomen, with its legs stretched out, and for periods as long as five minutes they remain absolutely quiet, without movements of any kind. During this period the pulse and respiration remain normal, but in marked intoxication marked bradycardia often develops. In several instances a pulse of 50 or 60 was present. Arrhythmia developed in one or two instances. In the event of recovery, all abnormal manifestations disappeared within from twelve to eighteen hours. Table 1 shows the

development of this intoxication in a dog and its disappearance under sodium chlorid solution.

In cats suffering from water intoxication, retching is violent, but vomiting is infrequent. In fact, convulsions often develop during, or soon after, the beginning of the first spell of retching or vomiting. Diarrhea is common. Stupor is marked. Convulsions are, perhaps, somewhat less violent than in dogs and are succeeded, as a rule, by asthenia and stupor. If animals survive they appear to be normal within a few hours (Table 2).

TABLE 2.—WATER INTOXICATION IN A CAT

Time	Weight, Kg.	Water Intake, C.c.	Temperature, C.	Remarks
8:45 a.m.	3.0	125	36.5	
9:15 a.m.	...	125		
9:45 a.m.	...	125		
10:15 a.m.	...	125	....	Vomited
10:45 a.m.	...	125		
11:15 a.m.	...	125	....	Salivated
11:45 a.m.	3.4	125	....	Vomited
12:15 p.m.	...	125		
12:45 p.m.	...	125	....	Ataxic
1:15 p.m.	...	125		
1:45 p.m.	3.5	125	37.0	
2:15 p.m.	...	125		
2:45 p.m.	3.7	125	37.0	
2:48 p.m.	...	...	....	Typical convulsion; head retracted, running movements of legs, eyes dilated, respiration shallow and rapid, and asthenia and stupor
2:55 p.m.	...	...	....	About 15 c.c. fluid obtained with stomach tube; death during night

TABLE 3.—WATER INTOXICATION IN A RABBIT

Time	Weight, Kg.	Water Intake, C.c.	Temperature, C.	Remarks
9:30 a.m.	1.7	100	36.5	Distilled water at body temperature
10:15 a.m.	...	100	....	Normal
11:15 a.m.	...	100		
11:45 a.m.	...	100		
12:00 m.	2.1	...	....	Salivated; ataxic convulsions lasting two minutes
12:15 p.m.	2.1	...	37.0	
1:05 p.m.	2.1	...	....	Found dead

In rabbits, retching and vomiting are usually absent. They develop a staggering gait, become asthenic, eventually lie down and become very sick. Diarrhea is absent, as a rule, but diuresis is marked and salivation is common. Stupor develops rather than coma. The convulsions approach in violence those occurring in the dog. Death may occur during either convulsions or stupor (Table 3).

In guinea-pigs, retching and vomiting do not develop; they have diarrhea, salivation and marked diuresis, become markedly ataxic and

spread their legs in a peculiar manner in an effort to support the body. They find great difficulty in walking, and often roll on their sides, the legs exhibiting marked running movements. Abdominal distention, as a rule, is marked. Stupor and convulsions ensue earlier and are more common than in larger animals (Table 4).

THE RELATIVE EASE OF INDUCING CONVULSIONS IN VARIOUS ANIMALS

In each species great variations are encountered with regard to individual susceptibility, that is, the readiness with which convulsions

TABLE 4.—WATER INTOXICATION IN A GUINEA-PIG

Time	Weight, Gm.	Water Intake, C.c.	Remarks
9:40 a.m.	771	20	Normal
10:30 a.m.	...	20	
10:55 a.m.	...	20	
11:25 a.m.	...	20	
11:55 a.m.	...	20	Normal
12:15 p.m.	...	40	
1:10 p.m.	891	..	Salivation
1:25 p.m.	...	40	
2:05 p.m.	...	40	
2:20 p.m.	...	..	Convulsion
2:55 p.m.	...	..	Regains feet but cannot walk; feet spread out in attempts to walk
3:10 p.m.	924	..	Weight at death 924 gm., an increase of 153 gm.; nothing in stomach at necropsy; edema of lungs

TABLE 5.—WATER INTOXICATION IN DOGS

Dog	Weight, Kg.	Water, C.c.	Percentage of Body Weight	Time Elapsing	Gain in Weight, Kg.	Percentage Increase	Remarks
3	6.2	3,000	48.2	4 hours, 50 minutes	0.4	6.6	Convulsions; recovered
4	6.3	3,900	62.0	6 hours, 30 minutes	0.7	11.1	Died
5	7.1	5,250	83.0	8 hours	0.4	5.6	Recovered; experiment repeated the next day
5	6.9	2,450	35.5	3 hours	0.5	7.2	Convulsions; water continued; weight at death, 8.4 kg.; drained 625 c.c. fluid from stomach and intestines
6	4.4	2,800	63.6	5 hours, 45 minutes	0.5	7.6	Water continued 6.75 c.c.; died; weight at death, 5.1 kg.

occur. In the dog, vomiting unquestionably tends to postpone the onset of convulsions. To a lesser extent this is also true of the cat. In rabbits and in guinea-pigs the water ingested is practically all assimilated and hence water toxicity develops somewhat earlier. Occasionally, individual dogs are markedly resistant to water intoxication. This may be due to recent access to an abundant supply of salt. Table 5 presents the important data for a group of dogs and Table 6 for cats, rabbits and guinea-pigs.

CHANGES IN WEIGHT AND THEIR INTERPRETATION

Difficulty is encountered in ascertaining the true significance of the increases in weight. Obviously, it is impossible, prior to the administration of water, accurately to determine the amount of fluid present in stomach and intestines.[20a] The weight indicated at any time during an experiment, or at the end, represents total weight only, and fails to differentiate between water assimilated and that which still remains in the gastro-intestinal tract. The stomach tube may reveal the amount of water in the stomach and whether or not there is sufficient to occasion gastric distension.

TABLE 6.—WATER INTOXICATION IN CATS, RABBITS AND GUINEA-PIGS

Rabbit	Weight, Kg.	Water, C.c.	Time, Hours	Gain in Weight, Kg.	Increase, per Cent.	Remarks
1	1.9	700	5.25	0.5	26.3	Typical convulsions; died next night
2	2.5	500	4.50	0.3	12.0	Convulsions; recovered
2	2.5	500	3.42	0.2	8.0	Convulsions; recovered
3	1.7	400	3.58	0.3	17.6	Convulsions; died
Guinea-pig	Gm.			Gm.		
1	513	220	3.42	269	52.2	Convulsions; died; weight at death 782 gm.
2	771	220	5.00	...	19.8	Convulsions; died; weight at death 924 gm.
3	515	90	2.00	50	9.7	Convulsions; died, 25 c.c. of fluid
4	490	200	3.00	105	21.0	Convulsions; died
5	510	215	2.45	98	19.00	Convulsions; died, 20 c.c. of fluid
Cat	Kg.			Kg.		
1	3.9	1,250	5.00	0.1	25.6	Convulsions; died
2	3.0	1,725	6.00	0.7	23.3	Convulsions; died
3	2.9	1,200	5.00	0.7	24.0	Convulsions; recovered
3	2.8	800	3.33	0.6	21.0	Convulsions; died
4	2.4	500	2.00	0.3	12.0	Convulsions; died
5	1.8	1,400	7.25	0.9	50.0	Convulsions; died
6	3.1	700	3.58	0.7	22.0	Convulsions; recovered
7	3.0	900	4.50	0.6	20.0	Convulsions; recovered

In many instances the water content of the intestines was determined at the necropsy, but owing to the fact that the amount in the intestines prior to the administration of water was not known, these figures are of but limited significance.

EXPERIMENTAL INDUCTION OF SUBACUTE WATER INTOXICATION IN RABBITS

Subacute water intoxication can readily be induced in rabbits. Water up to one-fourth of the body weight, given daily by stomach tube and in divided doses,[8] is tolerated over periods of from two to three weeks without evidence of untoward symptoms. Water in amounts of from 300 to 333 c.c. for each kilogram of body weight daily results, in the course of from one to two weeks, in the development of subacute water intoxication (Table 7).

20a. Under proper preliminary conditions intestinal content of water may be rather uniform. Stomach contents may be removed before starting the experiment. Hence these difficulties may, perhaps, not be insurmountable.

In the rabbit, the symptoms of subacute poisoning do not differ essentially from those of acute poisoning. Salivation first appears and this is accompanied by listlessness or lack of liveliness and often by ataxia; diuresis is marked and continuous, but the stools retain their normal consistency and their pellet-like form. The animal huddles into a corner and exhibits no interest in its surroundings. Weakness

TABLE 7.—CHRONIC WATER INTOXICATION IN RABBITS

Rabbit	Date, 1922	Weight, Kg.	Water Intake, C.c.	Urine Output, C.c.	Remarks
6-B	4/26	2.9	675	675	250 c.c. for each kilogram a day in three doses
	4/27	...	675	675	
	4/28	...	675	675	
	4/29	...	675	640	
	4/30	...	225	300	
	5/ 1	...	675	665	
	5/ 2	...	675	650	
	5/ 3	...	675	600	
	5/ 4	...	675	625	
	5/ 5	...	675	600	
	5/ 6	...	675	640	
	5/ 7	...	225	270	
	5/ 8	...	870	775	Dose increased to 300 c.c. for each kilogram a day
	5/ 9	...	870	810	
	5/10	...	870	850	
	5/11	...	870	800	
	5/12	...	870	820	
	5/13	...	870	800	Salivated
	5/14	...	290	275	Markedly salivated, ataxic
	5/15	3.2	290	...	Convulsions at 9:30 a. m.; apparently recovered, but died next night; no evidence of pneumonia at necropsy
8-B	5/ 6	2.9	540	500	225 c.c. for each kilogram a day in three doses
	5/ 7	...	180	200	
	5/ 8	...	870	800	Dose increased to 300 c.c. for each kilogram
	5/ 9	...	870	790	
	5/10	...	870	800	Possibly slight salivation
	5/11	...	870	795	
	5/12	...	870	850	
	5/13	3.1	870	815	Salivated
	5/14	...	290	300	Markedly salivated and ataxic
	5/15	...	...	...	Animal found dead in the morning with every indication of having died in convulsions; head retracted; no signs of pneumonia found at necropsy
9-B	5/ 6	2.1	495	450	About 225 c.c. for each kilogram a day in three doses
	5/ 7	...	165	180	
	5/ 8	...	630	300	Dose increased to 300 c.c. for each kilogram a day
	5/ 9	...	630	300	
	5/10	...	630	600	
	5/11	...	630	500	
	5/12	...	630	610	
	5/13	...	630	600	
	5/14	...	210	200	
	5/15	...	630	595	
	5/16	...	630	600	
	5/17	...	630	600	
	5/18	...	630	590	
	5/19	2.4	210	...	Salivated and stupid; convulsion and death at 2 p. m.; no evidence of pneumonia at necropsy

becomes marked and a state of stupor supervenes. Convulsions, similar in every respect to those of acute water poisoning, develop. The head is markedly retracted and this position may persist even after death. Subsequent to the convulsions, weakness progresses and helplessness becomes extreme. The animal may lie for an hour at a time on its side without moving. Micturition becomes involuntary. Death may occur suddenly during convulsions, or may come on gradually, super-

vening in the course of the stupor, coma or asthenia. A condition of stupor or coma may persist for three or four days prior to the death of the animal. Recovery may follow discontinuance of water excess.

NOTES ON THE PATHOLOGIC FINDINGS IN ANIMALS WITH ACUTE WATER INTOXICATION

Dr. Robertson has studied the tissues from several of these animals and submits the following report:

Results of postmortem studies on the animals used for experimentation, with a few exceptions, have revealed a notable absence of any specific pathologic changes. Such a result might reasonably be expected. The fulminating character of the clinical phenomena both in the rapidity and violence of their course strongly suggests such a speedy alteration in the metabolic activities of the vital cells of the body that few or no changes in the physical appearances of the cells or tissues can be detected. Pertinent analogies to this conclusion are presented by definite organic intoxications which produce alterations in structure only in inverse proportion to the time element and rarely in direct proportion to the violence of the symptoms.

At the first two examinations made on dogs who had succumbed to violent convulsions in a few hours, the only striking change that could be noted was a marked edema of the connective tissues around the portal vein and the area of distribution of its larger branches within the liver. The liver, itself, presented on section a moist surface as did also the kidney and there was slight edema of the upper portion of the mesentery. There was no marked increase of fluid on the surface of the brain although the brain itself was distinctly moist.

Miscroscopic examination of these tissues only served to emphasize the gross appearances. There was no definite edema of cells in the kidney, brain or liver, and no definite microscopic alterations could be identified. The connective tissues in the cortices of the kidneys, around the distribution of the portal vein, particularly its larger branches, and around the vessels of the brain showed distinct edema. In the two first cases this edema was marked in the substance of the liver.

Succeeding postmortem examinations on both rabbits and dogs were surprising because of the lack of consistency in the findings. Occasionally, the edema was again distributed as just indicated, but often it was almost entirely confined to the kidney, although there were always definite signs of increase of fluid within the brain substance. Uniformly in all cases the kidney was abnormally moist and microscopically showed evidences of interstitial edema, but careful study of the cells did not reveal in any instance significant or uniform change.

In this connection it is interesting to note that the same appearance of excessive moisture in the pulp of the kidney and liver has been observed in human postoperative cases when the fluid intake had been pushed evidently beyond the ability of the patient's excretory capacity.

DISCUSSION

Although the amount of water administered is extremely large in most instances, the gain in weight is, by contrast, strikingly small. There is adequate provision against too great absorption. A large water intake results in free diuresis and, in dogs and sometimes in cats, in profuse vomiting. In order to produce the severe intoxication, an intake of

more than enough water to compensate for the rapid loss of fluid is necessary. Not the fluid ingested, but the amount absorbed and assimilated is in all probability responsible for the toxicity.

In searching for an explanation of the development of the foregoing symptoms, the effect of the following procedures and conditions has been investigated since it was thought that they might possibly be concerned, etiologically, in the production of convulsions: (1) repeated passage of the stomach tube; (2) gastric distention; (3) absorption of digestive products and of toxins from the gastro-intestinal tract; (4) the rôle of the liver; (5) ligation of ureters; (6) administration by rectum; (7) intravenous injection and hemolysis; (8) hydremia; (9) edema of brain and increased intracranial pressure, and (10) effect of administration of sodium chlorid.

Repeated Passage of the Stomach Tube.—Control experiments involving the passage of the tube twenty times, at half hourly intervals, were carried out on dogs. No untoward effects were noted.

Gastric Distension.—The symptoms were believed to be due, perhaps, to gastric distension, and an attempt was made to prove this by ascertaining the amount of water in the stomach by means of the stomach tube. In dogs, cats, rabbits and guinea-pigs, attempts were made to withdraw fluid from the stomach immediately before, or after, convulsions. In most instances, the amounts withdrawn appeared to be entirely too small to have resulted in marked distention. In some instances, convulsions developed during attempts to vomit, but in others, onset was delayed until long after the vomiting attack. In many instances, in animals dying during convulsions, immediate necropsy showed but little fluid in the stomach.

If distension were the cause of the convulsions they should follow the administration of equivalent quantities of 0.8 per cent. sodium chlorid solution. But sodium chlorid solution administered to rabbits and to dogs in double these amounts failed to produce convulsions or any of the significant manifestations of water intoxication. I believe that sufficient evidence has been accumulated through such controls to justify the opinion that gastric distention is not the important factor in the production of water intoxication. However, since this intoxication has developed only in animals to which water was administered by mouth, the factor of distention cannot yet be entirely dismissed from consideration.

Absorption of Digestive Products and of Enzymes from the Gastro-Intestinal Tract.[21]—In order to determine the part played by too rapid

21. These experiments were carried out at the suggestion of Dr. F. C. Mann, and the operations involved were performed by Dr. Mann or members of his staff.

absorption of digestive products from the gastro-intestinal tract, dogs were first subjected to water abstinence experiments. The animals were subjected to two and four day periods of water fasting after which the intoxication was produced, attention being given to the ease with which it developed. In other experiments, an excess of water, 1,500 c.c. each day, was given for two day periods prior to the introduction of toxicity. The results of these experiments are set forth in Table 8. As far as these experiments go there is no evidence of absorption of toxic substances from the gastro-intestinal tract.

The Rôle of the Liver.[21]—Inasmuch as at necropsy the liver showed evidences of edema, it seemed desirable to determine whether or not the liver played an important part in this intoxication. Consequently,

TABLE 8.—Effect of Previous Fasting, Water Abstinence and Water Excess on the Development of Water Intoxication in Dogs

Dog	Weight, Kg.	Water, C.c.	Time, Hours	Gain in Weight, Kg.	Increase, per Cent.	Remarks
14	4.4	2,700	5.75	0.5	11.3	Died; weight 5.1 kg.; fluid in stomach 175 c.c.
15	6.8	3,750	7.00	0.5	7.6	Fasted two days; convulsions; recovered
15	5.6	3,850	7.16	0.4	7.1	Fasted four days; convulsions; recovered
16	4.8	4,125	9.00	0.8	16.6	Fasted two days; convulsions; recovered
16	4.2	2,250	4.25	0.5	11.9	Fasted four days; convulsions; recovered
17	4.5	2,700	8.00	0.3	6.6	Fasted two days; convulsions; recovered
17	3.8	2,600	6.00	0.3	7.9	Fasted four days; convulsions; recovered
18	6.1	1,800	3.50	0.5	8.2	Fasted two days; convulsions; recovered
18	6.0	2,400	4.00	0.4	6.6	Fasted four days; convulsions; recovered
19	5.9	3,600	5.16	0.6	10.1	Convulsions; recovered
19	5.7	3,300	5.00	0.7	12.2	Water abstinence four days; no different from first experiment; died
20	3.3	1,200	2.00	0.5	15.1	Water abstinence four days; died
21	5.2	3,300	6.00	0.7	18.4	Forced intake of 1,500 c.c. water each day for two days before experiment; convulsions; recovered
22	5.0	3,750	7.00	0.8	16.0	Intake previously forced as in above experiment; convulsions; recovered

attempts were made to produce water intoxication in some of Mann's dogs with Eck's fistula. The symptoms of poisoning developed in all respects as in normal animals and no difference was observed in the facility with which the intoxication developed.

The Effect of Ligation of Ureters.—All attempts to produce water intoxication in dogs with ligated ureters failed, probably because of excessive vomiting. In order to prevent vomiting in one of these dogs, a tube was fastened permanently into the duodenum and through this water in large quantities was introduced. Diarrhea resulted, but no manifestations of water intoxication. Similar results were obtained on administering water to a normal dog through a duodenal fistula.

The Effect of Water Administered by Rectum.[21]—Water was given to dogs by rectum in large quantities, and although the administration was continued at times until water was actually vomited from the mouth, in no instance did water intoxication develop. Warm water

resulted in relaxation of the sphincter, while cold water occasioned discomfort to the animals and hence its administration was discontinued. Thus, one dog which had previously exhibited convulsions after receiving 3,500 c.c. of water, when administered by mouth, was subsequently given 6 liters of water at 35 C. by rectum during the course of six hours. No symptoms of water intoxication developed. The reason for these results is not clear and further studies along these lines are necessary.

Intravenous Injection of Water and the Development of Hemolysis.—Distilled water was slowly administered intravenously to two rabbits. The first rabbit died within ten minutes after receiving 25 c.c. and the second died within one hour and ten minutes after receiving 95 c.c. In both instances, marked hemolysis resulted, but in neither case did water intoxication develop. A dog weighing 7.2 kg. was given intravenously 1,275 c.c. of tap water during a period of two hours and fifteen minutes. Marked salivation, retching, and polyuria resulted. The blood showed hemolysis and the urine was tinged with hemoglobin but water intoxication did not develop.

Hydremia.—The rôle of hydremia was studied in the previous experiments of Larson, Weir and Rowntree, which showed that water intoxication developed in certain animals subsequent to using the extract of the posterior lobe of the pituitary gland without demonstrable dilution of the blood and without demonstrable increase of the plasma or blood volume. Further studies along these lines are contemplated.

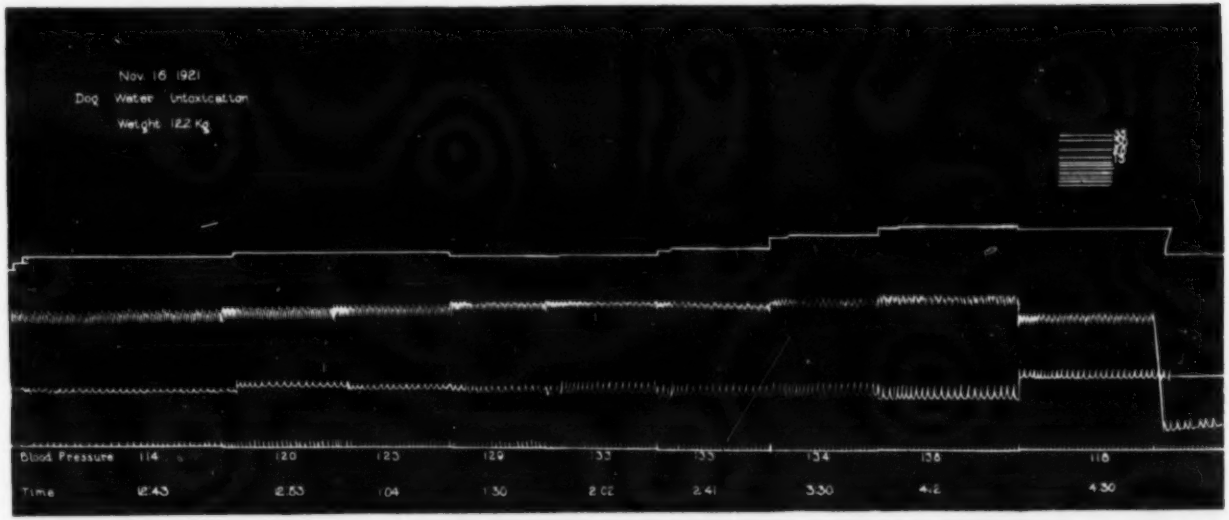
Edema of the Brain and Increased Intracerebral Pressure.—The marked cerebral disturbances, convulsions, stupor and coma led us to suspect an increase in intracerebral pressure. This was strengthened by the pathologic findings in some animals. The work of Weed and McKibben,[22] of Cushing and Foley,[23] of Foley and Putman,[24] and of Sachs and Belcher [25] on the changes of cerebral pressure, following the administration of hypotonic and hypertonic sodium chlorid solution intravenously, also suggested this possibility. It seemed desirable, therefore, to determine by actual measurement whether or not increased intra-

22. Weed, L. H., and McKibben, P. S.: Pressure Changes in the Cerebrospinal Fluid Fllowing Intravenous Injection of Solutions of Various Concentrations, Am. J. Physiol. **48**:512-530, 1919. Weed, L. H., and McKibben, P. S.: Experimental Alteration of Brain Bulk, Am. J. Physiol. **48**:531-558, 1919.

23. Cushing, H., and Foley, F. E. B.: Alterations of Intracranial Tension by Salt Solutions in the Alimentary Canal, Proc. Soc. Exper. Biol. & Med. **17**:217-218, 1920.

24. Foley, F. E., and Putnam, T. J.: Effect of Salt Injection on Cerebrospinal Fluid Pressure and Brain Volume, Am. J. Physiol. **53**:464-476, 1920.

25. Sachs, E., and Belcher, G. W.: The Use of Saturated Salt Solution Intravenously During Intracranial Operations, Preliminary Report, J. A. M. A. **75**:667-668 (Sept. 4) 1920.



Record obtained from a case of water intoxication, showing the respiration, blood pressure and intracranial pressure (upper curve).

cranial pressure accompanied the development of water intoxication. Through the assistance of Dr. Meek of the University of Wisconsin, the intracranial pressure of a dog with water intoxication was determined by utilizing the cannula devised by Lowenhart. A tracing from our one flawless experiment demonstrates that an increase in intracerebral pressure can result. Table 9 contains the details of this experiment. These findings are in keeping with those of Weed and McKibben, who demonstrated swelling of the brain through openings in the skull following intravenous injection of hypotonic solution (water), and of Ebaugh and Stevenson,[26] who made measurements of the intracranial pressure changes in a patient with epilepsy. On administering 4 or 5 liters of tap water by mouth for a period of one and one-fourth hours, an increase in intracranial pressure corresponding to 20 mm. of water was registered. In one instance Ebaugh and Stevenson administered

TABLE 9.—PROTOCOL ON DOG 101, 12.2 POUNDS IN WEIGHT

9:30 a.m.	Pulse 84, temperature 97.6 F., respiration 26; ether by tracheal tube started; dog voided 20 c.c. of urine; tambour inserted inside of skull; cannulas inserted into femoral veins; apparatus adjusted
12:45 p.m.	Pulse 132, temperature 96.8 F., respiration 42; water administered * and tracings started
12:45 to 3:50 p.m.	Water in quantities of 200 c.c. introduced every fifteen to thirty minutes; total amount introduced, 2,500 c.c.; abdomen considerably distended
4:18 p.m.	Stomach drained of 1,525 c.c.; pulse had varied from 120 to 132 throughout this period
4:25 p.m.	400 c.c. of water administered; pulse 120
4:30 p.m.	Animal killed; tambour calibrated; total water intake 3,200 c.c.; drained from stomach 1,525 c.c.; urine in bladder 100 c.c.; drained from stomach and intestines 400 c.c.; blood lost 150 c.c.; calculated water retention about 1 liter

* All distilled water administered at temperature between 38 and 40 C.

as much as 8 liters during the course of six hours. The patient complained of fulness, frequency of urination, fulness in the head, tinnitus and headaches, and felt as though an attack were impending.

Effect of Administration of Sodium Chlorid.[27]—It would appear reasonable to consider a disturbance in osmotic relationships and in salt water equilibrium of the brain and nervous system as important features in water intoxication, especially in relation to the nervous manifestations. At any rate, recognition of the increased intracerebral pressure led to experiments involving the use of hypertonic salt solution in an attempt to prevent or overcome convulsions. In early experiments it had already been determined that water intoxication could not be produced through the intravenous administration of large quantities of

26. Ebaugh, F. G., and Stevenson, G. S.: The Measurements of Intracranial Pressure Changes in an Epileptic and Its Experimental Variations, Bull. Johns Hopkins Hosp. **31**:440-447, 1920.

27. Hypertonic sugar solution (50 per cent.) is also effective, but acts more slowly.

0.8 per cent. sodium chlorid solution, even when the injections of salt solution were made in the early stages of true water intoxication.

Hypertonic sodium chlorid solution was administered to a group of dogs in various stages of water intoxication. In some instances the dogs in stupor, coma or convulsions showed striking improvement within from ten to fifteen minutes after the administration of the sodium chlorid solution; in fact, in many instances, the animals appeared to be practically normal within from one-half to one hour. The induction of water intoxication by the continued use of water becomes a matter of extreme difficulty after a previous administration of 10 per cent. salt

TABLE 10.—Effect of the Administration of Sodium Chlorid Solution on Water Intoxication

Dog	Weight, Kg.	Water by Mouth, C.c.	Time, Hours	Gain in Weight, Kg.	Increase, per Cent.	Remarks
11	6.0	2,350	4.0	0.9	15.0 ataxic	1,450 c.c. of 0.8 per cent. sodium chlorid solution intravenously; no convulsions
23	5.1	2,050	5.0	0.5	9.8 ataxic	55 c.c. 10 per cent. sodium chlorid solution intravenously; no convulsions
23	5.0	3,750	8.0	0.6	12.0 ataxic	50 c.c. 10 per cent. sodium chlorid solution intravenously; no convulsions
24	4.8	2,250	5.0	0.6	12.5 ataxic	50 c.c. 10 per cent. sodium chlorid solution intravenously; no convulsions
24	4.6	3,375	8.25	0.5	10.8 ataxic	50 c.c. 10 per cent. sodium chlorid solution intravenously; no convulsions
25	8.7	3,650	4.0	0.6	6.9	Convulsions followed by 90 c.c. 10 per cent. sodium chlorid solution intravenously; immediate recovery; paralysis of hind legs developed later
26	5.6	3,600 1,500	6.0 2.0	0.5	9.1	Convulsions; twitching; 65 c.c. 10 per cent. sodium chlorid solution intravenously; immediate improvement; paralysis of hind legs developed later
27*	4.7	2,000	3.5	0.6	12.7	Convulsions, followed by 50 c.c. 10 per cent. sodium chlorid solution intravenously; walking about fifteen minutes later; apparently normal in about one and one-half hours
29*	10.8	6,100	5.5	0.8	7.4	Convulsions; 80 c.c. 10 per cent. sodium chlorid solution intravenously; walked within ten minutes; apparently normal one and one-fourth hours later

* The administration of 4,500 c.c. and of 10,450 c.c. of sodium chlorid solution, respectively, to these two dogs failed to elicit any symptoms of water intoxication.

solution. It is, therefore, established that hypertonic sodium chlorid solution is effective in preventing or overcoming water intoxication (Table 10).

Excessive accumulation of water may occur as intercellular or intracellular edema. Water may accumulate in the body as an intercellular edema of the dependent parts, or as anasarca with free fluid in the large cavities of the body, without toxicity manifesting itself. In healthy animals increased intracerebral pressure and at times cerebral edema may arise as a result of excessive water ingestion, and is perhaps responsible for most of the phenomena herein described. Whether or not the edema of liver, kidney, and intestinal wall is of any pathologic significance has not been determined as yet. The possibility still exists

that edema of the intestinal wall may so damage the specific absorption of the intestinal epithelium that toxic products from the canal may enter directly into the blood stream. It is peculiar that to date this intoxication could be produced only by water administered by stomach tube. This fact renders difficult an exact explanation of the mechanism involved.

CONCLUSIONS

1. In man and animals (dog, cat, rabbit and guinea-pig) water ingested in excess of the ability of the organism to excrete it leads to water intoxication.

2. Water intoxication is manifested by restlessness, asthenia, polyuria, frequency of urination, diarrhea, salivation, nausea, retching, vomiting, muscle tremor and twitching, ataxia, tonic and clonic convulsions, frothing at the mouth, helplessness, stupor and coma.

3. The convulsions are general in character, of extreme violence and in the main resemble those of strychnin poisoning. They may recur at intervals of a few minutes.

4. Water intoxication terminates in death unless the excessive intake is discontinued.

5. Water intoxication may be acute, ending in death in from four to twelve hours, or subacute, lasting for some days. Subacute intoxication results from smaller amounts of water continued over a longer period of time.

6. Water intoxication is accompanied by, and is probably due, in part at least, to increased intracerebral pressure; this in turn is probably a manifestation of disturbance in the salt water equilibrium of the central nervous system.

7. Water intoxication can be prevented, alleviated or cured by the timely intravenous administration of hypertonic sodium chlorid solution.

THE BENZOATE TEST FOR RENAL FUNCTION. II*

F. B. KINGSBURY, PH.D.

MINNEAPOLIS

The use of ingested sodium benzoate as a test for renal function was first described by Swanson and me, in a preliminary report before the Federation of American Societies for Experimental Biology, in December, 1920. The full report was published in August, 1921.[1] In June, 1921, Snapper[2] published a report of work along similar lines. He found that after ingesting 5 gm. of sodium benzoate, the normal person on a porridge diet eliminated about 75 per cent. of it in the form of hippuric acid in the course of six hours. Lewis[3] had previously found a much more rapid elimination of hippuric acid under similar conditions, and this was verified by Kingsbury and Swanson. For this reason, it is believed that Snapper did not obtain all the hippuric acid eliminated in the test specimens of urine, and that these low results were due to the failure of his analytic method. However, Snapper's findings that the rate of hippuric acid elimination after the ingestion of sodium benzoate in 5 gm. doses was markedly less in persons suffering from nephritis than in normal individuals, but was little if any less in pneumonia patients and those having complete obstruction of the common bile duct and biliary fistula, are in general accord with the results of Kingsbury and Swanson.

Early results with the benzoate test gave evidence that it was sensitive and would probably indicate early disturbances of renal function. The findings given in this paper confirm this view. Sufficient data had already been obtained to show that, in well marked nephritis, the benzoate tests were always low, but such results were of little value to the clinician who already had made a thoroughly satisfactory diagnosis without the aid of the test. In borderline cases of possible disturbances of renal function, the benzoate test has proved to be of value, and it is mainly to its application in this type of cases that the later discussion will be devoted.

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* From the biochemical laboratory of the University of Minnesota Medical School.

* A preliminary report was made before the Society of Biological Chemists, Inc., in Toronto, Canada, December, 1922.

1. Kingsbury, F. B., and Swanson, W. W.: The Synthesis and Elimination of Hippuric Acid in Nephritis: A New Renal Function Test, Proc. Am. Soc. of Biol. Chemists **15**: 4 (Dec.) 1920; Arch. Int. Med. **28**: 220 (Aug.) 1921.

2. Snapper, I.: The Elimination of Hippuric Acid, Nederl. Tijdschr. v. Geneesk. **1**: 3044 (June) 1921.

3. Lewis, H. B.: The Synthesis and Rate of Elimination of Hippuric Acid After Benzoate Ingestion in Man, J. Biol. Chem. **18**: 225 (July) 1914.

As originally described, the test determines the three-hour output of hippuric acid after the ingestion of 2.4 gm. of sodium benzoate. With the exception of ruling out fruit from the diet during the time of the test, no conditions as to the intake of food or water during the test were prescribed. In the present work, such conditions were specified, and all the results given in this paper were obtained in benzoate tests carefully regulated and therefore uniform. The hourly elimination of hippuric acid during the three hours of the test was studied with persons in normal health and those presenting pathologic conditions, but it was found that nothing was gained in making the test in this manner. If the test was made in a two-hour period followed by a one-hour period, more information as to the ability of the kidney to excrete hippuric acid under the conditions of the test could be obtained; for in some pathologic cases in which a normal or nearly normal result was obtained for three hours, the two-hour elimination was definitely below normal, while the third hour elimination was sufficient to bring the total for three hours up to a normal value.

METHODS

Since many fruits contain benzoic acid or substances which may be converted into it in the body, they must be omitted from the diet before and during the period of the test. The patient is denied fruit at the evening meal on the day before the test. On rising the patient voids urine, and immediately thereafter drinks a solution of 2.4 gm. of sodium benzoate in about 100 c.c. of water. The container is rinsed with about 200 c.c., and this is also drunk. At the end of one hour, 200 c.c. of water is drunk, making a total water intake of 500 c.c., and at the end of two hours the first sample of urine is collected. The second specimen of urine, representing the third hour of the test, is collected one hour later. Both specimens of urine are preserved, unless they can be analyzed immediately. Preservation is effected by adding about 10 drops of a 10 per cent. solution of thymol in chloroform to each specimen; 15 c.c. of 2 per cent. nitric acid to the two-hour specimen, and 7 c.c. of the same solution to the one-hour specimen. The total volume of each specimen must be measured and an aliquot part taken for analysis. I have used the method previously described [4] for all the tests reported in this paper, with the slight modification of using half quantities of urine and all other materials necessary, keeping the time element for the various operations the same. The method as originally described was designed for use with any sample of urine, and, to be adequate for twenty-four hour normal urines in which the

4. Kingsbury, F. B., and Swanson, W. W.: A Rapid Method for the Determination of Hippuric Acid in Urine, J. Biol. Chem. **48**:13 (Sept.) 1921.

concentration of hippuric acid was low, required the use of 50 c.c. for analysis. The case with benzoate test specimens is different, for the concentrations of hippuric acid are usually so much greater that 25 c.c. are sufficient for analysis. In both the normal and pathologic series of tests, the method of making the test was uniformly as described. The sodium ethylate used in titrating the resulting benzoic acid is standardized against pure benzoic acid in chloroform solution, with phenolphthalein as indicator. The calculations are simple: 2.4 gm. of sodium benzoate is taken as equivalent to 2 gm. of benzoic acid. The hippuric acid resulting from the ingestion of benzoate is determined as benzoic acid, and the amount of this found in a test specimen of urine divided by 2 and multiplied by 100 gives the percentage of elimination.

EXPERIMENTAL DATA

It was necessary to make a larger series of determinations on normal subjects since the series already reported was rather small and contained no two-hour elimination values. The results are shown in Table 1. Medical students were the subjects mainly, but a few values obtained from patients known to be free from any renal disturbances are included. Several of the freshman medical students made tests on themselves, including the necessary analyses, as part of their regular work in physiologic chemistry. Their figures, checked by analyses made in this laboratory, are included in the series. In this connection, it is pointed out that the analytic work involved in making these tests is as easily and successfully handled by students as any other method of analysis required in their course. It will be noted that the average two-hour excretion of hippuric acid under the conditions of the test for forty-four normal individuals is 82 per cent. of the ingested dose of sodium benzoate and the third-hour excretion is 16 per cent. The limits for the two-hour test are from 70 to 91 per cent., and for the third hour, from 32 to 8 per cent. The average total three-hour output is 98 per cent., which agrees closely with the value, 97 per cent., found by Swanson and myself, under conditions which were not so closely prescribed with respect to the time when the test was made, and the amount of water ingested. It is also to be noted that the previous series was made on a smaller number of normal individuals, and that the hippuric acid was determined by the method of Folin and Flanders.[5]

In Table 1 are also shown the two and one hour volumes of urine in the normal test specimens. In about 50 per cent. of the normal two-hour tests, a marked diuresis is noticed. The actual concentration

5. Folin, O., and Flanders, F. F.: A New Method for the Determination of Hippuric Acid in Urine, J Biol. Chem. **11**:257 (April) 1912.

of hippuric acid in each two-hour specimen has been calculated (not shown in the table), and varies from 0.32 per cent. to 3.14 per cent.

It will also be seen that the dose of sodium benzoate per kilogram of body weight varied from 26.7 mg. in Subject 14, who weighed 90 kg., to 50 mg. in Subject 11, who weighed 48 kg.

TABLE 1.—*Normal Benzoate Tests*

Subject	Sex*	Weight, Kg.	Hippuric Acid Excreted			Urine 2 Hours, C.c.	Doses of Sodium Benzoate per Kg. of Body Weight, Mg.
			2 Hours, per Cent.	3 Hours, per Cent.	2 Hours, Gm.		
1	♂	68	91	102	2.67	123	35.3
2	♂	73	89	98	2.56	289	32.9
3	♂	68	88	96	2.58	...	35.3
4	♂	66	92	102	2.70	...	36.4
5	♀	65	86	96	2.52	...	36.9
6	♂	61	82	99	2.41	506	39.4
7	♂	70	87	100	2.55	286	34.3
8	♂	67	83	94	2.44	190	35.7
9	♂	82	86	102	2.52	340	29.3
10	♂	61	87	98	2.55	350	39.3
11	♀	48	75	100	2.20	650	50.0
12	♂	60	76	98	2.22	109	40.0
13	♀	51	78	97	2.29	360	47.0
14	♂	90	87	96	2.55	395	26.7
15	♂	70	75	101	2.20	355	34.3
16	♂	70	81	98	2.38	298	34.3
17	♂	61	78	98	2.29	153	39.3
18	♂	71	88	99	2.58	100	33.8
19	♂	64	89	96	2.35	144	37.5
20	♂	77	87	98	2.55	146	31.2
21	♂	70	88	103	2.58	204	34.3
22	♂	54	73	91	2.15	...	44.4
23	♂	61	78	100	2.29	95	39.3
24	♂	61	81	95	2.38	480	39.3
25	♂	73	86	101	2.56	158	32.9
26	♂	73	83	100	2.44	152	32.9
27	♂	66	73	89	2.14	118	36.4
28	♂	77	91	105	2.65	271	31.2
29	♂	70	92	102	2.70	325	34.3
30	♂	65	81	99	2.38	415	36.9
31	♂	88	84	106	2.46	248	27.3
32	♂	70	74	96	2.17	113	34.3
33	♂	73	76	93	2.23	71	32.9
34	♂	..	85	99	2.49	390	
35	♂	71	81	104	2.38	650	33.8
36	♂	64	84	98	2.46	126	37.5
37	♂	..	87	96	2.55	615	
38	♂	73	84	99	2.46	650	32.9
39	♀	..	81	99	2.38	300	
40	♀	..	71	89	2.08	122	
41	♂	..	90	102	2.65	840	
42	♂	..	83	105	2.44	465	
43	♀	..	70	100	2.05	498	
44	♀	..	72	104	2.11	480	

* In this column, ♂ indicates male; ♀, female.

In twenty-one of the normal tests, the three-hour output of hippuric acid when no benzoate had been ingested was also determined. This was done for the first three hours of the morning on one day. On the following day, benzoate tests were made, and the amount of hippuric acid which was so found, independent of the sodium benzoate ingested, was in each case subtracted from the values given by the tests. These data are shown in Table 2. Although these results indicate that control experiments made in this way might increase the accuracy of the

benzoate test, I am not prepared to modify the view expressed in the first paper on this subject that such experiments are practically unnecessary when the test is made in the way described, because of the great variability in the dose of sodium benzoate per kilogram of body weight and the difficulty in collecting test samples of urine with an accuracy which would warrant it. In the direction of increasing the accuracy of this test, all these factors must be considered.

As to what constitutes a normal test, I think that a two-hour test with elimination of less than 70 per cent. and a three-hour test with elimination less than 90 per cent. should be regarded as low, and the tests recorded in this paper have been judged on this basis. In cases,

TABLE 2.—*Normal Benzoate Tests Corrected*

Subject	Total 3-Hour Benzoate Test, per Cent.	Three-Hour Normal Morning Urine. Hippuric Acid as Benzoic Acid, Gm.	Corrected Benzoate Test, per Cent.
6	99	0.06	96
7	100	0.14	93
8	94	0.08	90
9	102	0.12	96
10	98	0.10	93
12	98	0.15	90
13	97	0.15	90
14	96	0.23	85
15	101	0.10	96
16	93	0.10	88
17	98	0.12	92
18	99	0.16	91
19	96	0.06	93
21	103	0.12	97
22	91	0.03	90
23	100	0.15	93
28	105	0.09	101
31	106	0.11	100
32	95	0.22	84
35	104	0.08	100
38	99	0.09	95

a few of which have occurred, in which the elimination in a two-hour test is low but is followed by a third hour elimination which is sufficiently high to make the total for three hours of 90 per cent. or better, unless there is good evidence of marked delay in the passage of materials from the stomach into the intestines which could account for this by delaying the absorption of the sodium benzoate, it seems necessary to attribute this result to a slightly lowered renal function. In normal tests in which by mistake the urine is collected in a one-hour period followed by a two-hour period, the results to be expected are a nearly even partition between the two periods of the total excretion of hippuric acid for the three hours.

Two experiments carried out on a normal subject are of interest in connection with the test. The first experiment shows the effect of drinking large quantities of water, and the second, the effect of the ingestion of a large amount of cranberries. The results of the first

experiment are shown in Table 3. It will be seen that by drinking 1,850 c.c. of water during the first two hours of the test, the excretion of hippuric acid can be raised from a normal average value of about 80 to 85 per cent., with a water intake of about 500 c.c., to 100 per cent., the value for a three-hour test.

The effect of eating 240 gm. of cranberries with 100 gm. of sucrose, for the evening meal, on the output of hippuric acid for the next few hours is shown in Table 4. As will be seen, there is little increase in the output of hippuric acid over the normal for the first three hours. The bulk of hippuric acid is formed and excreted during the next eleven hours, and the rate of excretion has become nearly normal again

TABLE 3.—*The Effect on the Benzoate Test of Drinking a Large Quantity of Water*

Time	Water Ingested, C.c.	Urine, C.c.	Excretion, per Cent.	Remarks
11:17 a. m.	600	...	...	2.4 gm. sodium benzoate ingested
11:47 a. m.	500	302	25	
12:17 a. m.	250	496	64	
12:47 a. m.	250	387	80	
1:17 p. m.	250	298	100	

TABLE 4.—*Effect of Eating Cranberries in the Normal Subject*

Time	Urine Voided, C.c.	Hippuric Acid Excreted, Gm.	Remarks
6:00 p. m.	...	.....	240 gm. of cranberries boiled with water, and 100 gm. of sucrose, ingested
7:00 p. m.	90	0.170	
8:00 p. m.	363	0.150	
9:00 p. m.	31	0.109	
11:00 p. m.	178	0.642	
8:00 a. m.	358	1.773	
11:00 a. m.	779	0.358	

within fourteen hours. Under normal conditions, cranberries, which are relatively rich in benzoic acid, could be eaten in large quantities at the evening meal without appreciably affecting the results of the benzoate tests made the following day on normal subjects. This would probably apply equally well to the ingestion of fruits. With subjects suffering from pathologic conditions, it could not be assumed that the ingestion of large amounts of cranberries or fruit at the evening meal preceding the test would be without effect on the test itself. For this reason, the procedure of ruling out fruit as outlined above was strictly adhered to.

TESTS ON HOSPITAL PATIENTS

These were carried out in the University Hospital, with the cooperation of the department of medicine. All laboratory data, with the

exception of the benzoate tests, were obtained from the hospital. In Table 5 are shown the summarized data from thirty-nine patients. The fact that elimination in the benzoate test is always low in nephritis has already been shown,[1] and is confirmed by the results presented in this paper. When the diagnosis of this condition is clear cut, there seems to be little need of making benzoate tests. The value of this test lies in showing the degree of impairment of renal function early in glomerulonephritis, nephrosis, pyelonephritis and arteriosclerosis of the kidney. It is also useful in determining the degree of improvement in function following the acute renal injury in toxemia of pregnancy. The details of cases will be limited to numbers 41, 42, 43, 48, 54, 56, 58, 60, 67 and 68. The diagnoses of these cases were made by Dr. George E. Fahr of the department of medicine, who kindly furnished data of certain other tests of renal function which he had made. These are the water excretion test of Volhard,[6] the determination of the constant of Austin, Stillman and Van Slyke,[7] MacLean's urea concentration test[8] and the phenolsulphonephthalein test of Rowntree and Geraghty.[9]

REPORT OF CASES

CASE 41.—*Diagnosis: Toxemia of pregnancy.* On entrance to the hospital, the patient showed edema of the face and lower extremities, and a blood pressure, 190 systolic, and 110 diastolic. Examination of the urine revealed granular and hyaline casts and a relatively large amount of albumin. Blood urea nitrogen and creatinin at this time were 23 mg. and 3 mg. respectively, in 100 c.c. of blood. Four phenolsulphonephthalein tests resulted in 85, 69, 65 and 65 per cent. elimination in two hours. About one month after entrance to the hospital, at the beginning of labor, the blood pressure was 160 systolic, and 125 diastolic. At about this time, there was a considerable amount of albumin in the urine. A benzoate test six days before parturition resulted in 50 per cent. elimination in two hours, with a total for three hours of 69 per cent., definitely low. At the time of the patient's discharge from the hospital, the blood pressure was normal as was also the urea nitrogen of the blood. Urinary findings were normal.

CASE 42.—*Diagnosis: Subchronic glomerulonephritis.* The blood pressure was 140 systolic, and 82 diastolic. Examinations of the urine revealed albumin and casts constantly present. Two phenolsulphonephthalein tests were normal, elimination being 66 and 63 per cent. in two hours. The blood showed a retention of urea. The results in the benzoate test on three occasions were constantly low. The result in MacLean's urea concentration test was 0.9 per cent. The

6. Volhard, F., and Fahr, T.: Die Brightsche Nierenkrankheit, Berlin, 1914, pp. 121, 126.

7. Austin, J. H.; Stillman, E., and Van Slyke, D. D.: Factors Governing the Excretion Rate of Urea, J. Biol. Chem. **46**:91 (March) 1921.

8. MacLean, H., and de Wesselow, O. L. V.: On the Testing of Renal Efficiency, With Observations on the "Urea Coefficient," Brit. J. Exper. Pathol. **1**:53 (Feb.) 1920.

9. Rowntree, L. G., and Geraghty, T. L.: An Experimental and Clinical Study of the Functional Activity of the Kidneys by Means of Phenolsulphonephthalein, J. Pharmacol. & Exper. Therap. **1**:579, 1910.

TABLE 5.—*Summary of Benzoate Tests in Thirty-Nine Patients*

Case	Sex*	Age	Benzoate Test		Phenolsulphonephthalein, 2 Hrs., %	Blood (100 C.c.)			Blood Pressure		Diagnosis	Albumin	Remarks
			2 Hrs. per Cent.	3 Hrs. per Cent.		Urea Nitrogen, Mg.	Creatinin, Mg.	Glucose, Mg.	Systolic	Diastolic			
30	♀	50	..	40	28	29	1.9	102	190	110	Chronic nephritis	—	Discharged; condition unchanged
				40	18								
31	♀	34	..	82	..	13	1.1	90	...	...	Chronic pulmonary tuberculosis	—	Discharged; condition unchanged
32	♀	60	..	87	49	18	2.6	195	165	100	Hypertension; obesity	—	Discharged; improved
33	♀	36	..	10	15	40	4.0	131	..	...	Chronic nephritis	—	Discharged
34	♂	62	..	10	..	52	5.4	129	...	...	Chronic glomerulonephritis	+	Discharged
						56	4.4	122					
35	♂	27	..	22	trace	55	8.0	111	180	112	Chronic glomerulonephritis; cardiac hypertrophy	+	Died 1/22/22
						54	8.5	117					
						45	8.7	135					
						38	5.1	120					
						30	5.4						
36	♂	14	..	66	95	23	1.8	129	130	70	Chronic nephritis	+	Discharged
37	♂	23	..	15	0	95	9.1	120	...	...	Chronic nephritis	+	Discharged
38	♂	52	..	37	..	28	3.2	132	...	...	Acute nephritis; cardiac disease	+	Discharged
39	♂	52	..	44	..	34	2.6	81	164	120	Arteriosclerosis; chronic cardiac hypertrophy; auricular fibrillation	+	Died 10/22/21
									150	130			
40	♂	23	..	74	..	24	3.8	93	176	120	Acute nephritis	+	
41	♀	24	50	69	85	23	3.0	...	190	110	Toxemia of pregnancy; nephrosis	+	Discharged; improved
					60				100	125			
					65								
					64								
					60								
42	♀	28	65	82	66	32	2.7	87	140	82	Subchronic glomerulonephritis	+	Discharged
			50	71	63		1.9						
			59	85									
43	♀	26	64	87	55	25	2.5	82	...	...	Toxemia of pregnancy; nephrosis	—	Discharged; improved
			75	95	55	23	2.3						
			76	93		21	2.9						
						11	1.7						
						10							
44	♂	50	19	30	15	42	4.6	100	...	...	Chronic glomerulonephritis	+	Discharged
45	♂	67	44	61	..	..	...	...	148	96	Chronic myocarditis; emphysema	+	Discharged
			28	48									
46	♀	50	57	74	56	20	2.1	78	178	138	Chronic nephritis; hypertension	—	Discharged; water excretory function impaired (Volhard's test)
			60	79	49								
47	♂	27	16	22	0	80	7.5	140	...	...	Chronic nephritis	+	Discharged
48†	♂	72	40†	101†	82	Normal	Normal	Normal	...	...	Duodenal ulcer	—	Discharged
49	♂	51	13	24	15	103	11.0	110	...	...	Hydronephrosis; pyelonephritis; carcinoma of rectum	+	Phenolsulphonephthalein and benzoate tests on left kidney alone; died
			44	62	24	91	9.0	80					
						46	3.0						
						67	5.0	137					
						126	8.0						

50	♂	..	87	95	..	..	...	...	...	...	Normal, no disease	—	
51	♂	53	..	13	..	..	...	...	...	...	Chronic nephritis	+	
				14	6	47	4.9	108					
			16	23	8	87	2.6	325					
			18	29									
			11	17									
52	♂	27	39	48	..	..	...	...	...	...	Lobar pneumonia	—	Discharged
53	♀	32	88	95	..	..	...	...	...	...	Normal as far as kidneys are concerned	—	Discharged
54	♂	32	57	74	58	50	2.9	80	...	...	Pyelonephritis; bronchopneumonia	+	Died
			35	50	24	21	2.5	89					
						36	2.3	80					
55	♀	21	86	97	..	..	...	...	...	...	Normal as far as kidneys are concerned	—	
56	♀	36	56	80	40	19	2.0	...	...	...	Hypertension	—	Delivered, 1/18/22; discharged
			66	86	38	16	2.0	91					
			54	75	63	16	2.2	90					
					46	12							
57	♀	16	72	94	..	18	2.0	64	...	...	Goiter; normal as far as kidneys are concerned	—	Discharged
58	♀	27	23	36	5	51	6.0	100	138	110	Subchronic glomerulonephritis	+	Discharged
					6								
59	♂	21	49	77	67	21	2.1	80	175	120		+	Discharged
					43	26	3.0						
					54	22	2.8						
60	♀	52	70	89	63	12	1.9	100	190	124	Hypertension; arteriosclerotic kidney	—	Discharged
			57	84	54								
61	♀	47	12	31	36	25	2.3	80	...	...	Chronic nephritis; hydronephrosis of right kidney	+	Died
					14								
62	♂	24	57	74	..	23	2.0	112	...	...	Left kidney removed; clinical evidence of other kidney being involved	+	Alkaline reserve reduced; benzoate test after nephrectomy
			5	14	7	49	4.0	118					
						51	5.0						
						63	6.0						
63	♂	26	76	87	46	..	...	...	...	...	Tuberculosis of left kidney; kidney removed; no clinical evidence of other kidney being involved	—	
64	♂	36	67	89	42	..	...	...	...	...	Addison's disease	..	Died 3/13/22
					54								
65	♀	24	34	61	20	19	1.7	80	...	...	Edema and clinical indications of renal involvement	+	Delivered 3/14/22; benzoate test 2 days previously; discharged
66	♀	38	61	77	58	14	2.0	...	...	...	Abnormal pregnancy; toxemia of pregnancy	+	Discharged
67	..	..	35	61	52	..	...	...	190-200	...	Hypertension		
68	..	..	70	100	79	10	1.9	...	148 in bed, 224 when up	...	Early state of hypertension		
					88								

* In this column, ♂ indicates male; ♀, female. † In 1¾ hours. ‡ In 6¼ hours.

normal kidney under the conditions of this test effects a concentration of urea of 2 per cent. or more. The constant of Austin, Stillman and Van Slyke was also low, 1.8, the normal constant being 7.5 plus or minus 3. The condition of the patient at the time of discharge from the hospital showed no improvement. The close agreement between the findings by the benzoate test and those of MacLean and Van Slyke and co-workers is to be noted. This is in harmony also with the blood findings. The phenolsulphonephthalein test failed to indicate any renal injury.

Case 43.—This patient on admission to the hospital had a blood pressure of 165 systolic, and 120 diastolic. Examination of the urine revealed many granular and hyaline casts and a large amount of albumin. The blood showed a slight retention of urea. A phenolsulphonephthalein test at this time resulted in an elimination of 36 per cent. in two hours. Shortly after parturition, a benzoate test resulted in 64 per cent. elimination in two hours, with a total for three hours of 87 per cent., slightly, but definitely, low. A phenolsulphonephthalein test four days previously was normal. The blood at this time contained 10 mg. of urea nitrogen and 1.7 mg. of creatinin in 100 c.c. Urinary findings, except for a very slight trace of albumin, were normal. Subsequently, two benzoate tests were normal; the urinary findings and blood pressure were normal, and the patient was discharged from the hospital. The diagnosis of this case was toxemia of pregnancy. It is to be noted that, at the time the blood findings had indicated a return to the normal condition, there was still a slight indication of renal insufficiency by the benzoate test. This was not shown by the phenolsulphonephthalein test.

Case 48.—*Diagnosis: Duodenal ulcer.* A lowering of elimination in the benzoate test would perhaps be expected in this case because of the possibility of the duodenal ulcers interfering with the normally rapid absorption of sodium benzoate. The benzoate test specimens, through an error, were collected one and three quarters and six and a quarter hours, respectively, after the ingestion of the 2.4 gm. of sodium benzoate. The values obtained, 46 per cent. in the first period and 101 per cent. for the total period, are low, but are probably not due to any impairment of renal function in this particular case.

Case 54.—*Diagnosis: Pyelonephritis.* On one occasion, high and on another occasion low elimination was shown in a phenolsulphonephthalein test. Results in the bezoate test were low on both occasions. There was a considerable retention of urea nitrogen in the blood, which was lowered somewhat by treatment. The constant of Austin, Stillman and Van Slyke, 2.8, was definitely low.

Case 56.—A pregnant woman infrequently gave slightly positive reactions in tests for albumin in the urine, and occasionally a hyaline cast was found. The systolic blood pressure was never below 190, even when the patient was resting in bed. On the administration of nitroglycerin, there was a rise in blood pressure. Results in Volhard's water excretion test were definitely low. There was no edema. Elimination in MacLean's test was 1 per cent., a definitely low result. Phenolsuphonephthalein output varied from 40 to 63 per cent. in two hours. The constant of Austin, Stillman and Van Slyke was 2.3, 2.3, and 2.8 on three occasions, all definitely low. Elimination in benzoate tests, one made before delivery and two afterward, was, respectively, 56 per cent. in two hours, with a total of 86 per cent. for three hours; 54 per cent. for two hours, with a total of 75 per cent. for three hours, and 66 per cent. for two hours, with a total of 86 per cent. for three hours, all results being slightly, but definitely, low. Urea and creatinin in the blood taken at the time of labor were in normal amount. Blood pressure findings after parturition showed a definite improvement in the patient's condition and were normal at the time the patient was discharged from the hospital. Data from the university dispensary showed this to be a case of hypertension.

CASE 58.—*Diagnosis: Subchronic glomerulonephritis.* Elimination in MacLean's test was 0.65 per cent., definitely low; phenolsulphonephthalein output on two occasions was 5 and 6 per cent. in two hours; elimination by benzoate tests 23 per cent. in two hours, with a total for three hours of 36 per cent.; the constant of Austin, Stillman and Van Slyke was 1.1 and 0.7 on two occasions, definitely low. There was a considerable retention of urea in the blood.

CASE 60.—*Diagnosis: Hypertension with arteriosclerotic kidneys.* There was a variation in the specific gravity of the urine of 1.002 and 1.016, with day and night volumes of 1,209 and 1,600 c.c., respectively. The systolic blood pressure was from 180 to 215 during rest in bed. Elimination in MacLean's test was 1.5 per cent., definitely low; the phenolsulphonephthalein output was 63 and 54 per cent. on two occasions. A urea nitrogen test of the blood showed no retention. The constant of Austin, Stillman and Van Slyke was 4 and 2.5 on two occasions, the first value being on the borderline of normality and the second low. Elimination by the benzoate test was normal on the first occasion, and slightly, but definitely, low on the second, agreeing closely with the findings by the constant of Austin, Stillman and Van Slyke.

CASE 67.—*Diagnosis: Hypertension.* The constant of Austin, Stillman and Van Slyke was 5, which is within normal range. The result with Volhard's water excretion test was low. MacLean's test, 1.8, was nearly normal, but results with the benzoate test were decidedly low, 35 per cent. for two hours, with a total of 60 per cent. for three hours. Systolic blood pressure ranged from about 190 to 200.

CASE 68.—This patient had shown a high blood pressure for the preceding four years, with a present systolic pressure of 224 when up and about, and 148 when in bed. Albumin and casts were found during the first pregnancy. Recently, a few casts and a trace of albumin had been noted. The eye-grounds indicated hypertension. Urea nitrogen and creatinin were at a normal level in the blood. The constant of Austin, Stillman and Van Slyke was normal (7.8); results in the benzoate test, Volhard's, MacLean's and the phenolsulphonephthalein test were all normal. This case was diagnosed as essential hypertension. It is to be noted that none of the renal function tests indicate any reduction of kidney sufficiency.

SUMMARY AND CONCLUSIONS

1. The benzoate test indicates the impairment of renal function early. There is a fairly close agreement in this respect with the water excretion test of Volhard, the urea concentration test of MacLean, and the constant of Austin, Stillman and Van Slyke, in the few cases in which the comparison was possible.

2. The benzoate test indicates renal insufficiency earlier than does a test of the urea content of the blood. Low results in benzoate tests have been noted in cases showing at the same time a normal concentration of urea in the blood. Normal indications in benzoate tests have not been obtained on patients whose blood showed at the same time a retention of urea. For this reason, it seems unnecessary to make urea determinations in the blood until benzoate tests have first been made and have shown a definite renal insufficiency.

3. The results of this paper confirm and extend those of Swanson and myself. Additional data have been presented on the test with normal individuals, by which to judge the results obtained with patients

ADDITIONAL OBSERVATIONS

Since this article was prepared, a paper by Morgulis, Pratt and Jahr [10] has appeared containing misleading allusions to the original work of Kingsbury and Swanson and criticisms of some of their conclusions.

These authors, by finding what was apparently free benzoic acid in the urine of patients with parenchymatous nephritis who had been given sodium benzoate by mouth, concluded that some benzoic acid had escaped conjugation with glycin. The claim was made that our "assumption" of the nonoccurrence of free benzoic acid in the urine in such cases was incorrect. We made no such assumption as this but determined the fact (see page 7 of our original paper [1]). This was done in a case of glomerulonephritis, the diagnosis of which was checked by necropsy findings and in a case of nephritis of the arteriosclerotic type which was also checked by necropsy, as well as in two so-called cardiorenal cases. After giving each of these patients the prescribed dose of 2.4 gm. of sodium benzoate, the three-hour urine specimens were analyzed by the Raiziss and Dubin [11] method for free benzoic acid (albumin having previously been removed by our procedure). The titration figures obtained were blanks inherent in the analytic procedure and did not represent any detectable amount of free benzoic acid. For ordinary 100 c.c. samples of urine such blanks were from 0.05 to 0.10 c.c. of one-tenth normal sodium ethylate. Using distilled water in place of urine, the same blanks were obtained.

In confirmation of this earlier work, an experiment was quite recently made on a case of glomerulonephritis which was fatal about one week after the benzoate test was made. This patient showed a marked retention of urea nitrogen, and necropsy subsequently proved that the diagnosis was correct. Sodium benzoate, 2.97 gm. (1.8 gm. per square meter of body surface) were given to this patient, and the three and the twenty-four hour output of hippuric acid determined. This amounted in three hours to 10 per cent. and in twenty-four hours to 60 per cent., in both cases being wholly in the form of hippuric acid as the determinations below show. Large samples, 170 c.c. and 250 c.c., respectively, of the three and the twenty-one hour specimens were analyzed by the method of Raiziss and Dubin after albumin had been removed. Five cubic centimeters of concentrated nitric acid for acidifying the urine specimens and approximately 100 gm. of ammonium sulphate were added and four extractions made with 50 c.c. portions of neutral, washed toluene. The combined 200 c.c. portions of toluene extract in each case were washed with 100 c.c. of the Folin-Flanders

10. Morgulis, S.; Pratt, G. P., and Jahr, H. M.: Hippuric Acid Synthesis as a Test for Renal Function, Arch. Int. Med. **31**:116 (Jan.) 1923.

11. Raiziss, G. W., and Dubin, H.: On the Estimation of Benzoic Acid in the Urine, J. Biol. Chem. **20**:125 (Feb.) 1915.

saturated salt solution, then filtered and titrated. The two titration figures obtained were 0.08 c.c. and 0.12 c.c. of one-tenth normal sodium ethylate. The blank on 200 c.c. of the same toluene similarly treated using water instead of urine was 0.10 c.c. No free benzoic acid was found, not even a determinable trace, although in the three-hour period the patient excreted 0.362 gm. of hippuric acid and in the following twenty-one hour period 1.836 gm. of hippuric acid. This is the type of nephritis which presumably is that designated by Morgulis and his co-workers as "parenchymatous," in which they claim that free benzoic acid was excreted.

Our explanation of the main source of error in the work of Morgulis, Pratt and Jahr is that they extracted some of the hippuric acid present, since chloroform, which they used for this purpose instead of toluene, is well known to have a solvent effect on hippuric acid, and the hippuric acid so extracted was titrated and called free benzoic acid. Possibly two other sources of error also crept into their work, for otherwise it is hard to explain the magnitude of the blanks which they mistook for free benzoic acid. The first is that of using acid samples of chloroform. Long experience on the part of one of us has taught that chloroform is a most uncertain substance in this respect unless carefully washed just prior to use; and the second is that of the spontaneous decomposition of hippuric acid with the resultant release of free benzoic acid in specimens of urine not carefully acidified. We used adequate amounts of 2 per cent. nitric acid which prevents this accidental hydrolysis, as Raiziss and Dubin have found, and which we have confirmed many times in this laboratory.

A NEW METHOD FOR ACCURATELY DETERMINING THE CLOTTING TIME OF THE BLOOD*

MORITZ F. PETERSEN, M.D.
AND
C. A. MILLS, PH.D., M.D.
Medical Fellow of the National Research Council
CINCINNATI

The coagulability of the blood is often one of the most important factors with which the clinician must deal. In all cases of bleeding, it is essential to determine whether the cause is a delayed coagulation of the blood or some other factor, such as local infection and injury of blood vessels. This is especially true in purpura, hemophilia, bleeding in the new-born and jaundice, and in preoperative examination of patients. An accurate method of estimating this property of the blood is therefore essential for the proper handling of such cases. For clinical use, the method must be simple and require little apparatus.

Many methods have been advocated to determine the clotting time, their very number indicating that none is quite satisfactory. A complete and comprehensive review of all these methods up to 1907 is found in a paper by Hinman and Sladen.[1] Since that time, a number of modifications of the old methods, and a few new ones have been described. We will consider only the fundamental shortcomings of these methods.

As regards the temperature factor, several investigators have shown the marked effect of the temperature on the clotting time, while Rudolph[2] goes so far as to say that there is one minute difference for each degree of change in temperature between 15 and 20 °C. Many of the methods in use disregard this important factor entirely, while others attempt to control it by means of water-bath devices. With the temperature uncontrolled, the methods lose most of their value even for comparative work, while all water bath devices are either too small to maintain a constant temperature, or are too complicated for widespread clinical use.

In the Brodie and Russell method[3] and its modifications, the factors of evaporation and agitation of the blood are added to the temperature

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* From the departments of pediatrics and medicine, University of Cincinnati Medical College and Cincinnati General Hospital.

1. Hinman, F., and Sladen, F. J.: Measurement of the Coagulation Time of the Blood and Its Application, Bull. Johns Hopkins Hosp. **18**:207, 1907.

2. Rudolph, R. D.: A Clinical Method of Estimating the Coagulation Time of the Blood, Am. J. M. Sc. **140**:807. 1910.

3. Brodie, T. G., and Russell, A. E.: The Determination of the Coagulation Time of Blood, J. Physiol. **21**: 403, 1897.

factor in producing sources of error. The ideal method would be one in which the end-point is determined by viscosity changes in the blood with a minimum of agitation, since agitation delays the gelation; and in which the blood is kept at or near body temperature from the time of drawing. These ends must be attained without complexity of procedure or apparatus, if the method is to be clinically useful.

During the last few months, one of us, in making studies of the clotting time under various conditions, found that none of the foregoing methods answered our needs fully, owing either to the complexity of the method, or its inaccuracy under varying external conditions; and we therefore sought for a simple yet dependable method that could be applied at any time or place with little difficulty.

The following method, which has now been used in hundreds of determinations, answers these requirements. Its sources of error are quite easily controlled, as we have determined by careful tests. The results, for practical and comparative purposes, are surprisingly accurate.

The method depends on the fact that blood ceases to flow back and forth in a capillary tube at the first sign of clotting. Capillary tubes of from 0.6 to 0.8 mm. inside diameter are drawn from clean glass tubing and cut into about 1¼ inch lengths. The blood is obtained from a stab wound of the finger or ear, the first drop being wiped off. The tube is touched to the second drop, and the blood is allowed to flow in by capillarity, leaving about one fourth inch unfilled. Time is counted from the appearance of the second drop over the wound. Some pressure, provided it is applied at a little distance from the wound, is permissible in getting the drop to form rapidly. After filling, and in order to secure a constant and definite temperature, the tube is placed in one of the creases of the palm and completely covered by closing the hand. This gives a uniform temperature, somewhat below that of the body (about 35 C.), and obviates the necessity of a water bath or chamber of any sort. By simply opening the hand slightly for observation when inverting the tube, one may note the end point without changing the temperature or disturbing the tube. The tube should be gently inverted every thirty seconds, and observation made of the time when the column ceases to move, on being so inverted. Jarring and shaking tend to prolong the clotting time and should therefore be avoided.

The diameter of the tube should be sufficient to allow a rather free flow of the blood when the tube is held upright just after filling. If the tube is too small, the attraction of the glass, a slight drying at the two ends of the blood column and an increase in the viscosity of the blood on cooling slightly all tend to impede the flow, with the result that the real end-point cannot be distinguished.

With a clotting time of approximately three minutes, the tube should be inverted every thirty seconds. When it is beyond from five to six minutes, it should be inverted every minute, and when less than two minutes, every twenty seconds. The simplicity of the method permits the making of two or three determinations without discomfort to the patient, so that results may be compared and averaged. As a rule, the different readings do not vary more than twenty seconds.

The normal clotting time with this method depends on several factors, such as the time of day when the determination is made, the length of time since the last meal and the nature of this meal. Mills and Nakayama [4] have found that the normal clotting time with no food in the gastro-intestinal tract is usually from three to three and a half minutes by this method. For from one to three hours after each meal, it is lowered to from one and one half to two minutes, rising again to

TABLE 1.—*Determination of Clotting Time*

	Clotting Time	
	Hr.	Min.
Sept. 10, 1922		
7:30 a. m. (before breakfast)	3	10
11:30 a. m. (only water since rising)	3	00
12:30 p. m. (luncheon)		
2:30 p. m.	2	40
5:30 p. m.	2	15
6:00 p. m.	3	00
Sept. 11, 1922		
8:00 a. m. (only water)	3	30
8:10 a. m. (breakfast)		
9:15 a. m.	2	00
11:45 a. m.	3	40

three minutes, usually before the next meal. So it is evident that the clotting time depends greatly on the time of making the determination, as shown in Table 1. It is advisable to determine the clotting time always at the same time of day, either before breakfast or just before some other meal. In this way, the clotting time, uninfluenced by digestion, food, etc., can be determined for comparative purposes over a long period of time. This clotting time, to which the blood reverts after each meal, may be termed the basal clotting time.

In Table 1 we submit the results of a few determinations demonstrating these statements.

To show that these are not accidental variations, we submit in Table 2, a series of determinations (Sept. 13, 1922) on the same individual, showing how constant the clotting time is under the same conditions.

Another series of determinations made on different individuals at the same time of day show only slight variations. All these persons

4. Mills, C. A., and Nakayama, Joseph: The Effect of Food Ingestion on the Clotting Time of the Blood, to be published.

ate lunch at about the same time, i. e., 12 m. to 12:30 p. m. The clotting times were taken about three and one half hours later, as shown in Table 3.

The method is reliable in giving similar results under like conditions, when the precautions mentioned earlier are observed. It does not give the true clotting time of the blood alone, since the method of obtaining the blood allows of an admixture of tissue juices from the wound edges.

TABLE 2.—*Constancy of Clotting Time*

Time	Clotting Time	
	Hr.	Min.
7:33 a. m.	2	50
7:40 a. m.	2	50
7:50 a. m.	2	50
7:53 a. m.	2	50
8:18 a. m.	2	50
8:40 a. m.	3	00

TABLE 3.—*Variations in Determinations on Different Individuals*

Subject	Time	Clotting Time	
		Hr.	Min.
Dr. P.	4 p. m.	2	00
Dr. P.	9 a. m.	2	55
Miss H.	4 p. m.	3	00
Miss N.	4 p. m.	3	00
Miss S.	4 p. m.	3	00

But, for practical purposes, this is just what is desired. Clinically, we are interested, not in the circulating blood so much as in the coagulation of the blood through injured tissue. The degree of protection afforded the body by the interaction of all the blood clotting factors is shown by this method and others of like nature.

The clotting time of the blood may be accurately determined by this means with such ease and simplicity that there no longer exists any good reason why clinicians everywhere, in hospital, office, or home, should not take advantage, in all indicated cases, of the knowledge thus to be gained.

THE INDUCTION OF PREMATURE CONTRACTIONS AND AURICULAR FIBRILLATION BY FORCED BREATHING

ASSOCIATED WITH A CHANGE IN THE LOCATION OF THE PACEMAKER *

FRED M. SMITH, M.D., AND WILLSON B. MOODY, M.D.
CHICAGO

Numerous attempts have been made to produce premature contractions in the experimental animal by the stimulation of the vagus and the sympathetic nerves. Rothberger and Winterberg [1] and Kuré [2] were perhaps most successful in these experiments. The former investigators employed combined stimulation of the vagi and the sympathetic, and the latter stimulated the sympathetic. Lewis [3] records one instance in which premature beats followed the stimulation of the left vagus on repeated occasions. In a later survey of the subject, Lewis [4] questions the interpretation placed by Rothberger and Winterberg on some of their curves, and calls attention to the very low percentage of positive results obtained by Kuré. He further points out that, in the large number of experiments in which he has stimulated the vagus under varying conditions, in only one instance did the extrasystoles seem to be related to nerve impulses. Lewis thus concluded that experimental observations did not demonstrate that an abnormal action of the cardiac nerves alone was responsible for the premature beat. He was, however, of the opinion that nerve impulses might provoke extrasystoles in the heart predisposed to the disorder. This conclusion was based on experimental investigations made by Levy [5] and Rothberger and Winterberg.[6] The former noted the appearance of premature contraction on stimulation of the sympathetic or on sectioning the vagi after the administration of chloroform. The latter produced premature beats by stimulation of the sympathetic

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* From the Medical Department of Rush Medical College.

1. Rothberger, C. J., and Winterberg, H.: Arch. f. d. ges. Physiol. **141**: 343-377, 1911.
2. Kuré, K.: Ztschr. f. exper. Path. u. Therap. **12**:389-459, 1913.
3. Lewis, Thomas: Heart **5**:247, 1913-1914.
4. Lewis Thomas: The Mechanism and Graphic Registration of the Heart Beat, New York, Paul B. Hoeber, 1920, p. 345.
5. Levy, A. G.: Heart **7**:105-110, 1918-1920.
6. Rothberger, C. J., and Winterberg, H.: Arch. f. d. ges. Physiol. **142**: 401-522, 1911.

following the use of barium chlorid. Each of the foregoing substances apparently increased the irritability of the heart, thus contributing to the appearance of the irregularity.

From the standpoint of auricular fibrillation, experimental observations on the reaction of the auricles to vagal stimulation are varied, and are apparently conflicting. It is generally known that stimulation of the vagi may alter the auricular action in auricular fibrillation.[7] The auricles dilate, and the movements become smaller and more rapid. In other instances of auricular fibrillation, vagal stimulation may be followed by a normal auricular mechanism.[8] On the other hand, the stimulation of the vagi has been observed to promote or induce an absolute irregularity in the normal by contracting auricles.[9] An auricular fibrillation has even been noted to follow the sectioning of the vagi. Lewis, Drury and Bulger [10] have recently confirmed the foregoing reactions with the exception of the last, and conclude that all are compatible with the circus movement of auricular fibrillation. The four cases presented herewith are of interest in that in each premature contractions were induced by forced breathing. In one, the premature beat appeared after administration of epinephrin. In two, auricular fibrillation followed the administration of epinephrin. In one of the latter, the absolute irregularity was at one time provoked by forced breathing.

REPORT OF CASES

CASE 1.—*Premature contractions induced by forced breathing and eliminated by atropin.* J. S., aged 31, complained of shortness of breath, palpitation and an occasional irregular action of the heart. He was extremely nervous. The cardiac symptoms dated back to military service. He stated that prior to that time his general health had been very good. His past history was negative for the infections that ordinarily induce cardiac disease. There was no history of real infection, and the Wassermann test on the blood was negative.

The examination was negative except for the heart. The cardiac impulse was well within the nipple line in the fifth interspace. A very faint diastolic murmur was heard to the left of the sternum in the third and fourth interspaces. The heart was extremely irritable. The rate increased to 140 per minute with the hopping test but subsided to 80, the original count, within two minutes. The systolic blood pressure was 130, the diastolic, 80. A premature contraction appeared regularly with forced breathing during expiration. The electrocardiogram taken during deep breathing showed a variation in the duration of the cardiac cycles from 0.68 to 0.95 second. The premature beat occurred during the height of vagal tone (Fig. 1, top). This irregularity was eliminated by atropin (Fig. 1, bottom). There was in addition some depression

7. Lewis, Thomas: Heart **1**:306, 1909-1910. Rothberger, C. J., and Winterberg, H.: Arch. f. d. ges. Physiol. Robinson, G. C.: J. Exper. Med. **17**:429, 1913.

8. McWilliams, J. A.: J. Physiol. **8**:296, 1887. Hirschfelder, A. D.: Bull. Johns Hopkins Hosp. **19**:322, 1908. Cushny, A. R.: Am. J. M. Sc. **141**:826, 1911. Garrey, W. E.: Am. J. Physiol. **21**:283, 1908.

9. Winterberg, H.: Arch. f. d. ges. Physiol. **122**:361, 1908.

10. Lewis, Thomas; Drury, A. N., and Bulger, H. A.: Heart **8**:141, 1921.

of the auricular wave during vagal inhibition. The auricular deflection was diaphasic in some instances, and was occasionally negative with a shortening of the P-R interval. The change in the auricular phase of the electrocardiogram persisted to some extent after the administration of atropin sulphate, one-fiftieth grain.

CASE 2.—*Premature contractions and idioventricular rhythm during forced breathing following administration of epinephrin.* W. K., aged 22, complained of nervousness and occasional cardiac irregularity. His past history was negative, and the Wasermann test of the blood was negative.

The apex impulse was 1 cm. outside the nipple line in the fifth interspace. A soft diastolic murmur was heard to the left of the sternum in the third and fourth interspaces. The sytolic blood pressure was 130, the diastolic, 70.

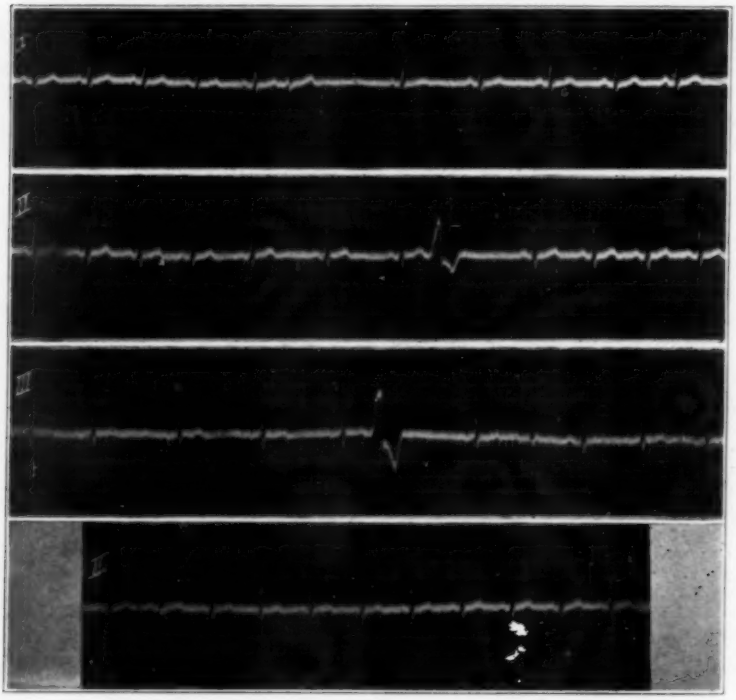

Fig. 1 (Case 1).—Top: The three leads were taken during forced breathing. The duration of the cardiac cycles in Lead I varies from approximately 0.68 to 0.95 second. In each lead is shown a premature contraction which appears during vagal inhibition. A change in the form of the auricular deflection is noted in Leads II and III. In Lead II, the second and fourth are depressed. The third seems diaphasic and the fifth is apparently negative. In Lead III, there is only one positive auricular wave, and it appears during the accelerated period. Bottom: Lead II was taken during forced breathing twenty minutes after the administration of atropin sulphate, one-fiftieth grain. The extrasystole has disappeared, but the change in the auricular deflection persists.

The initial electrocardiogram showed a regular rhythm (Fig. 2, top). The curve at the bottom was taken twenty minutes after the hypodermic administration of epinephrin, 10 minims (1:1,000 solution). Leads II and III show the effects of deep breathing. There are now periods during which there is a definite slowing of the cardiac rate associated with the onset of an idioventricular rhythm and the appearance of premature contractions.

CASE 3.—*Premature contractions during forced breathing, and auricular fibrillation following the administration of epinephrin.* F. P., aged 32, complained of an occasional vague distress in the precordial region. He was highly nervous, in this respect resembling very much the patients previously considered. His past history was negative and there was no venereal infection.

The heart was normal in size and there were no murmurs. Premature contractions appeared fairly regularly during forced breathing. They seemed to occur near the end of the greatest inhibition in the cardiac rate. The systolic

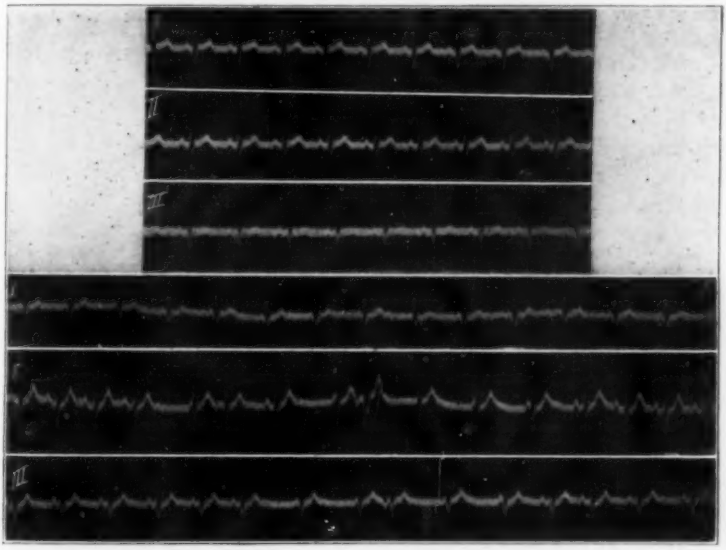

Fig. 2 (Case 2).—Top: Curve taken during forced breathing. Bottom: The electrocardiogram was taken twenty minutes after administration of epinephrin. Leads II and III show the effect of deep breathing. There are periods of inhibition in the cardiac rate during which there is an idioventricular rhythm and premature contraction.

blood pressure was 118, the diastolic, 80. The electrocardiogram verified these findings with regard to the extrasystole (Fig. 3, top). There was a greater variation in the duration of the cardiac cycles during forced breathing than in the preceding patient. The changes in the auricular deflection during the increased vagal tone were similar to those shown by the electrodiogram of the first patient considered. There was an occasional instance in which there was no evidence of auricular activity preceding the ventricular deflection. Following the electrocardiogram shown in Figure 3 (top), 10 minims (1:1,000 solution) of epinephrin hydrochlorid was given hypodermically. In about fifteen minutes, the auricles went into fibrillation (Fig. 3, bottom). Vagal

stimulation by forced breathing and by pressure on the eyes and the carotid sheaths apparently did not influence the absolute irregularity. The auricular fibrillation continued for about two hours.

CASE 4.—*Premature contractions and auricular fibrillation following deep breathing.* F. W., aged 39, consulted a physician because of attacks of rapid action of the heart. These attacks had occurred at infrequent intervals for about two years. They had repeatedly been observed to appear during periods of excitement and high nervous tension. He had recently been compelled to take a physical examination for a position, and had been fearful that he might

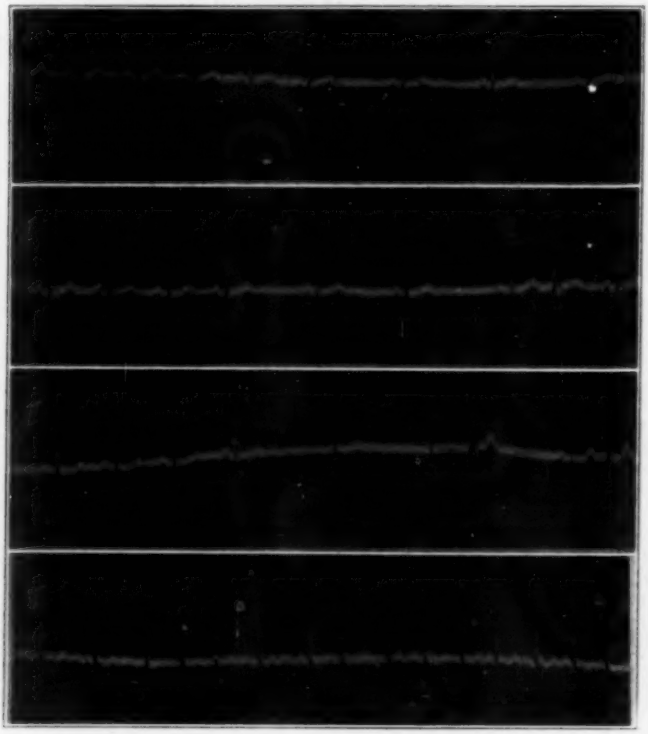

Fig. 3 (Case 3).—Top: The record was taken during forced breathing. In Leads II and III, premature beats appear near the end of vagal inhibition. Changes in the auricular deflection are also noted, particularly in Lead III. The fifth auricular complex is a slightly negative phase. In the sixth cardiac cycle, there is no evidence of auricular activity preceding the ventricular deflection. Bottom: Lead II shows an auricular fibrillation following the administration of epinephrin, 10 minims (1:1000 solution).

not pass the physical test because of the possible onset of the tachycardia. No sooner had he presented himself for the examination than an attack occurred. The examining physician noted that the cardiac rate was extremely rapid and the rhythm apparently absolutely irregular. The attack ended abruptly shortly after the examination.

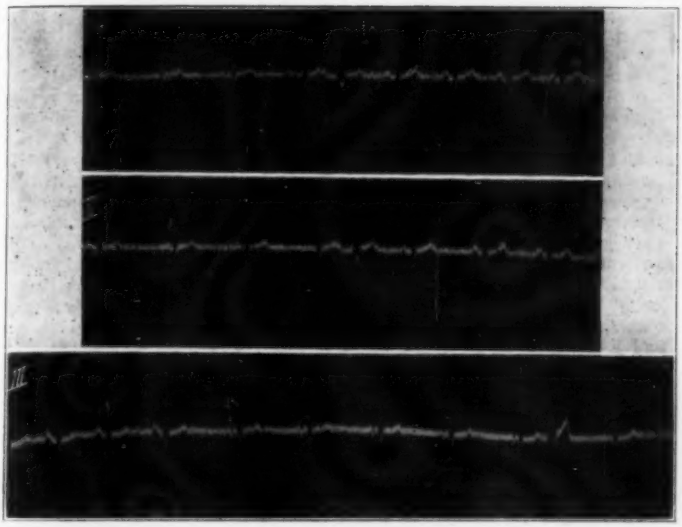

Fig. 4 (Case 4).—Leads I, II and III taken during forced breathing. In each lead a premature contraction occurs during the period in which there is an inhibition in the cardiac rate. Preceding the appearance of the extrasystole, there are changes in the form of the auricular deflection.

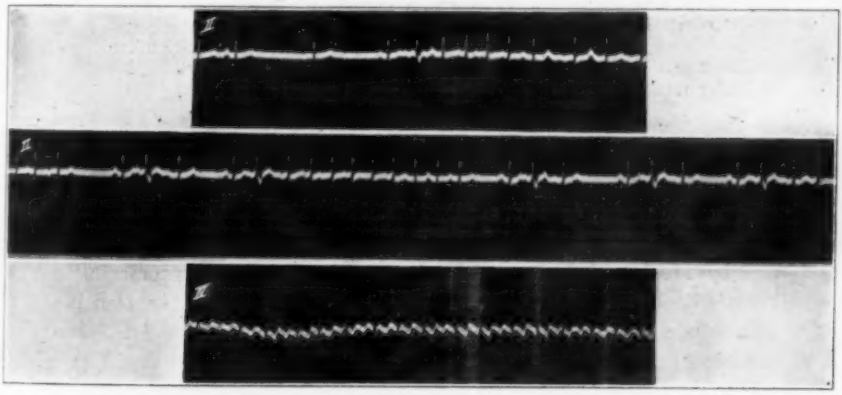

Fig. 5 (Case 4).—Top: Lead II: The onset of auricular fibrillation induced by deep breathing. Middle: Lead II: The auricular fibrillation induced by epinephrin was broken up into short paroxysms by combined pressure over the carotid sheaths and forced breathing. The normal auricular mechanism was restored for a few cycles during expiration. It is observed that premature contraction appeared during this period. It is to be further noted that the onset of the absolute irregularity is preceded by an extrasystole. Bottom: Lead II: The auricular mechanism resembles that of flutter. The record was taken after the administration of physostigmin, one seventy-fifth grain.

The general health had been very good. There was a history of typhoid fever in childhood, but no other serious illness, rheumatism, a relative freedom from sore throats, and no venereal infection. The Wassermann test on the blood and spinal fluid was negative. The teeth had recently been roentgen rayed. Five were found to have apical infections and were extracted. The patient was accepted for life insurance in 1920. The examining physician noted a rapid cardiac rate and requested that he return for another pulse reading.

The patient was more than 6 feet tall and weighed 190 pounds (86.4 kg.). He appeared to be in excellent general health. The physical examination was negative except for the heart, which was normal in size and without murmurs, but during ordinary breathing showed a slight waxing and waning of rate. The patient was requested to breathe deeply. Short attacks of rapid irregular heart action appeared during expiration (Fig. 5, top), persisting as long as the forced breathing was continued but subsiding as soon as normal respiration was established. The patient was very anxious about the condition of his heart. He had had little sleep for several nights and was extremely nervous. He was encouraged and told to forget the heart, and was asked to return in one week. He apparently placed absolute confidence in the advice and began at once to sleep soundly through the night. One week later, he returned for further observation. The nervousness had subsided and he had no further trouble with the heart. We were unable to produce the auricular fibrillation by forced breathing, but premature contractions occurred regularly at the height of vagal inhibition (Fig. 4). The patient was then given 10 minims (1:1,000 solution) of epinephrin, hypodermically. At the end of twenty minutes, an extremely rapid, irregular cardiac rhythm was precipitated by forced breathing. Unfortunately, the onset of the auricular fibrillation was not caught by the electrocardiograph. Later, on forced breathing, the irregularity occurred in short paroxysms (Fig. 5, center). The normal auricular mechanism was restored for a few cardiac cycles during the period of greatest vagal inhibition, produced by pressure over the carotid sheaths at the time of expiration. The patient was then given physostigmin, one seventy-fifth grain. The electrocardiogram taken twenty minutes later showed auricular flutter (Fig. 5, bottom). We may add that this patient also had changes in the auricular deflection of the electrocardiogram, with expiration during the period of normal auricular mechanism.

COMMENT

The changes that occurred in the auricular deflection of the electrocardiogram of three of these patients have been described by Wilson,[11] White[12] and others. Similar variations in the auricular wave have been produced experimentally in animals by Lewis and his co-workers[13] and by Meek and Eyster.[14] The mechanism of this phenomenon in man is dependent on an increased action of the vagus nerves on the sinus node over that on the lower rhythmical centers, and is comparable to that produced experimentally in animals by the stimulation of the right vagus. The rate of the sinus node is sufficiently decreased to permit the escape of the auriculoventricular node as the pacemaker.

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11. Wilson, F. N.: Three Cases Showing Changes in the Location of the Cardiac Pacemaker Associated with Respiration, Arch. Int. Med. **16**:86-97 (July) 1915.
12. White, P. D.: Ventricular Escape, Arch. Int. Med. **18**:244 (Aug.) 1916.
13. Lewis, Thomas; Meckins, J., and White, P.: Phil. Tr. Roy. Soc., London, Series B. **205**:375, 1914.
14. Meek, W. J., and Eyster, J. A. E.: Heart **5**:227-246, 1913-1914.

The migration of the pacemaker from the sinus to the auriculoventricular node may be sudden or gradual. If the former, there is an abrupt change in the auricular complex from a positive to a negative form, with a shortening of the P-R interval. If the latter, the auricular wave may be flattened or become diaphasic before it finally reaches the negative phase. During the intermediate changes from the positive to the negative form, the impulse may arise from both the sinus and auriculoventricular nodes. There is an occasional instance in which there is no evidence of auricular activity preceding the ventricular deflection. It is believed that under these circumstances the pacemaker may have migrated to a lower level in the auriculoventricular node, or there even may be an escape of an idioventricular rhythm.

The mechanism responsible for the change in the location of the pacemaker in the second patient is apparently different from that in the three patients previously considered. The opposing actions of the vagi and sympathetic nerves in the patient were well balanced under normal conditions even with deep breathing (Fig. 2, top). After the administration of epinephrin the action of these nerves was markedly deranged. It will be noted that there are periods of inhibition in the cardiac rate during which there is an escape of an idioventricular rhythm resulting in a dissociation of the auricles and ventricles (Fig. 2, bottom). It would seem that the phenomena might be explained on the basis of a combined stimulation of the vagi and sympathetic by the epinephrin, in which the abnormal action of the former is manifested chiefly on the sinus node, whereas that of the latter increases the inherent rhythm of the ventricles. In the experimental animal, an inhibition of the cardiac rate has frequently been observed following the administration of epinephrin. This was explained on the basis of vagal stimulation.

An idioventricular rhythm occasionally follows the administration of atropin. Wilson [15] and White [12] have each reported a patient in whom this phenomenon was observed. In each instance, there was a delayed conduction of the auriculoventricular bundle. The curves shown in Figures 6 and 7 are of particular interest in this connection, in that the auriculoventricular dissociation resulting from a recurring cardiac infection was later reproduced by administration of atropin. The electrocardiogram in the case of this child first showed a prolongation of the P-R interval similar to that in (Fig. 6, bottom). Later, there was an auricular ventricular dissociation (Fig. 6, top). After about two months, the sinus rhythm was again established (Fig. 6,

15. Wilson, F. N.: The Production of Atrioventricular Rhythm in Man After the Administration of Atropin, Arch. Int. Med. **16**:989 (Dec.) 1915.

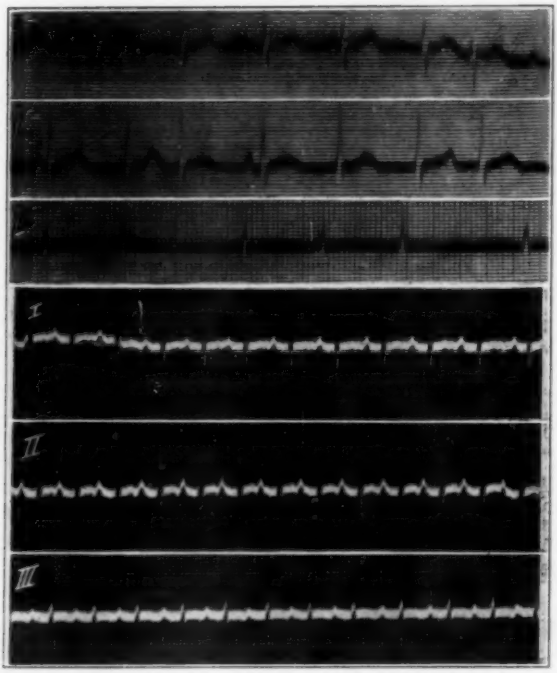


Fig. 6.—Top: Dissociation between the auricles and ventricles. In the first three cycles of Lead I, the ventricles are responding to sinus impulses. Bottom: A prolongation of the P-R interval.

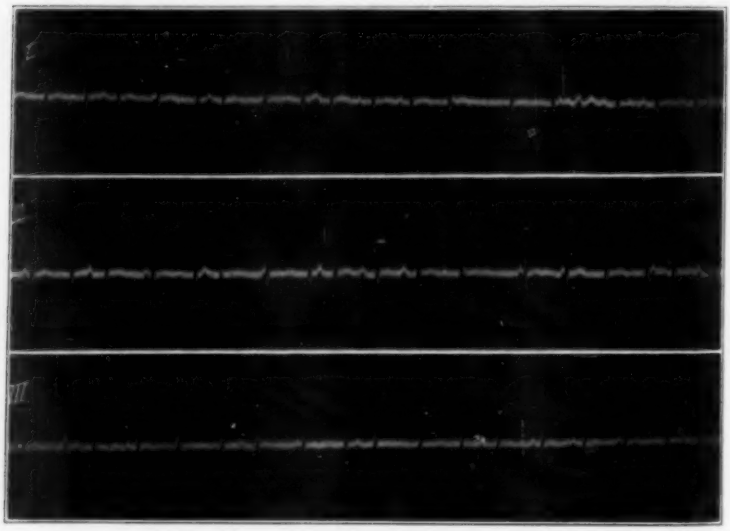


Fig. 7.—This curve was taken twenty minutes after the administration of atropin. The condition resembles that shown in Fig. 6 (top). In the middle of Lead II, there are three cycles of sinus rhythm.

bottom). At this time, the child was given 1/300 grain atropin sulphate, hypodermically. The electrocardiogram taken twenty minutes later showed an auriculoventricular dissociation (Fig. 7). Wilson has explained this reaction on the basis of an unequal distribution of the action of atropin on the vagus endings. He considered that those fibers which supply the auriculoventricular bundle were perhaps paralyzed first. This, in turn, permitted the escape of a ventricular rhythm, resulting in a dissociation of the auricles and ventricles. The observation in this patient suggests that vagus action on the auriculoventricular bundle might have been deranged by the infection.

In each of the first four patients, the premature contractions were induced by forced breathing. They regularly appeared during the period of the inhibition of the cardiac rate. It would thus seem that the stimulation of the vagi incident to deep breathing influenced the appearance of the irregularity. It would also seem that an increased sympathetic tone may perhaps be a contributory factor, since in one instance the premature beat appeared after the administration of epinephrin. It is very doubtful that the nerve stimulation was entirely responsible for the irregularity, since the patients, according to their history, were apparently predisposed to disorder. This conception is in accord with the results of experimental investigation.[16] It is to be recalled that the production of premature contractions in the experimental animal by stimulation of the cardiac nerves alone has been unsuccessful; whereas the results have been positive after the heart was predisposed to the disorder by the administration of chloroform and barium chlorid.

In two of the patients, paroxysmal auricular fibrillation was observed. Neither of these patients had the cardiac pathology usually associated with an auricular fibrillation. In each, the heart was apparently normal in size. In each instance, the absolute irregularity was induced by epinephrin. In one, the auricular fibrillation was at one time provoked by forced breathing. The latter feature was observed when the patient was extremely anxious about his condition. A few days later, after the nervousness had subsided, the irregularity could not be produced by deep breathing alone but only after it was induced by epinephrin. It is to be further recalled that the paroxysmal auricular fibrillation frequently occurred during periods of excitement. While the disorder was influenced by the strong inhibitory action of the vagi, it was also apparently dependent on the state of the sympathetic tone. Thus, when the sympathetic tone was high, vagal stimulation favored the entrance of the state of rapid reexcitation responsible for the auricular fibrillation.

16. Lewis, Thomas: Footnotes 5 and 6.

So far as we know, Stokes [17] has reported the only other instance in which forced breathing induced auricular fibrillation. An additional feature in our patient was the precipitation of the disorder by epinephrin and excitement. Kuré [18] has recorded a patient in whom paroxysmal tachycardia was induced by excitement. He was able to produce the tachycardia by compelling the child to concentrate on a problem in mental arithmetic. Lewis [4] states that he has observed similar but less striking examples of the latter feature. In this connection, it may be added that Galli [19] has reported an instance in which paroxysmal tachycardida followed the administration of atropin. The patient was, however, subject to the condition.

17. Stokes, K. H.: Heart **1**:297-305, 1909-1910.
18. Kuré, K.: Deutsch. Arch. f. klin. Med. **106**:33-46, 1912.
19. Galli: Heart **7**:111 (April) 1920.

THE RELATIONSHIP OF EXCESS OF URIC ACID IN THE BLOOD TO ECZEMA AND ALLIED DERMATOSES

BASED ON AN ANALYSIS OF OVER TWO HUNDRED CASES

JAY F. SCHAMBERG, M.D.
Director, Research Institute of Cutaneous Medicine

AND

H. BROWN, B. Sc.
Chemist, Research Institute of Cutaneous Medicine

PHILADELPHIA

The present study was undertaken for the purpose of shedding some light on the etiology of diseases of the skin of obscure origin. It was soon found that special interest was attached to the findings in eczema. For this reason, a special study was made of this disease, which comprises over one half of the analyses made.

Cases of eczema constitute almost one third of the cases of diseases of the skin. This disease commonly causes keen distress by intolerable itching. Sleep is interfered with, the nervous system greatly disturbed and life often made almost unbearable. The causative factors in the production of eczema have for a century been obscure. All sorts of hypotheses have been advanced, advocated, discussed, and most of them have been discarded to make way for new suppositions. The Vienna School under the leadership of Hebra held that the dominant causes of eczema were local, whereas the French school conjured up hereditary or acquired diatheses to explain the origin of this disease. It must be recognized that eczema is not a simple entity, but a type of reaction in the skin possessing certain clinical features. These features are not sufficiently distinctive to enable one to distinguish the etiologic factors involved. It is often impossible to differentiate between a chronic dermatitis due to local irritants and a true eczema of constitutional origin. There is an almost general agreement today concerning some causes of eczema. It is acknowledged that among etiologic factors may be classed intestinal toxemia, protein sensitization (both food and other proteins), endocrine disorders, disturbances of the nervous system, hyperglycemia, and other conditions. The older writers, particularly among English dermatologists, laid considerable stress on the association of gout and eczema. The urinary analyses and the laboratory data on which this origin of eczema was predicated were, however, regarded as so loose and unscientific as to lead to a progressively growing incredulity concerning this alleged relationship. In four out of six American treatises on dermatology published within recent years, no

mention of gout or uric acid in relation to eczema is made, and scant attention is paid to renal insufficiency.

FINDINGS IN CHEMICAL STUDIES OF THE BLOOD

As our blood analyses accumulated, it became evident that in the group of cases studied by us, the blood sugar was almost invariably within normal limits. The average content of sugar in 166 cases was 101 mg. It varied between 65 mg. and 160 mg. per 100 c.c. of blood. In two cases—a case of eczema and a case of psoriasis—it was 160 and 146 mg., respectively, but these figures although above the average were possibly not beyond normal limits. In only one case was the sugar content of pathologic significance. This was in a woman, 70 years of age, who had had generalized itching for twenty years, and who presented an erythematous eczema of the legs, with vulvar and vaginal pruritus. She had 273 mg. of sugar per 100 c.c. of blood. The urine was free from sugar, but there was a history that glucose had been found in the urine on former occasions. On a diabetic regimen, the pruritus promptly improved almost to the point of disappearance.

URIC ACID

In the course of our studies, it soon became evident that the most significant finding was a variation from the normal of the uric acid content. It is, of course, a matter of the greatest importance to possess an accepted standard of the maximum normal amount of uric acid in the blood.

In 1913, Folin and Denis [1] wrote that the normal uric acid content in healthy adults was usually between 2 and 3 mg. per 100 c.c., but that strictly normal persons might have as low as 1 mg. and as high as 3.5 mg., the differences probably depending in part on dietary factors. Nine years later, Folin [2] writes: "The maximum normal figure for uric acid may be perhaps given as 3 mg. per 100 c.c.* Others investigators have given estimates of the normal limits which are presented in the subjoined table.

In order to check our results, we examined the blood of seventeen presumably normal persons. It so happened that these were all young adults varying in age between 18 and 35 years. The uric acid content varied between 1.3 and 3.5 mg. and averaged 2.5 mg.

Of this number, one had 3.5 mg., one 3.4, one 3.2 mg. and two 3.1 mg. It is not known that all of these subjects were entirely normal,

1. Folin, O.: J. Biol. Chem. **14**:29, 1913.

2. Folin, O.: Physiol. Rev. **2**:460 (July) 1922; quoted from the article of Meyers, Fine and Lough (footnote 3).

* In a private communication received by us in April 1923, from Dr. Folin, he writes "The upper normal values for uric acid are probably a little higher than we have thought."

but they were taken at random among laboratory workers and presumably were normal.

In patients presenting themselves with various dermatoses, different findings are encountered. Of 163 patients, eighty-eight, or 53.6 per cent. had more than 3 mg. of uric acid. Fifty patients, or 30.5 per

TABLE 1.—*Normal Values of Human Blood in Milligrams per 100 c.c.*

Nonprotein Nitrogen	Urea Nitrogen	Uric Acid	Sugar	Authority
30-45	15-25	1.0-3.5	50-120	Gettler and Baker: J. Biol. Chem. **23**: 211, 1916
22-37	12-27	0.7-3.7	95-110	Folin and Denis: J. Biol. Chem. **14**: 29, 1913
30	.....	.....	.....	Greenwald: J. Biol. Chem. **21**: 61, 1915
19-39	6-20	.....	100-110	Bang: Biochem. Ztschr. **72**: 104, 1915
25-28	.....	.....	50-150	Taylor and Hutton: J. Biol. Chem. **22**: 63, 1915
23-44	12-27	.....	.....	McLean and Selling: J. Biol. Chem. **19**: 31, 1914
25-30	12-15	1.0-2.0	.....	Meyers and Fine: Post-Graduate, N. Y., 1914-1915
				Hohlweg: Med. klin. Wchnschr., 1915, p. 331
	10.8-25.2	.....	.....	Schwartz and McGill: Arch. Int. Med. **17**: 42 (Jan.) 1916
		2.5	.....	Moose and Zondek: München. med. Wchnschr. **62**: 1110, 1915
			90-110	Lewis and Benedict: J. Biol. Chem. **20**: 61, 1915
			90-130	Michaelis: Biochem. Ztschr. **59**: 166, 1914
			40-120	Strouse: Bull. Johns Hopkins Hosp. **26**: 211, 1915

TABLE 2.—*Blood Values from Normal Persons* *

No.	Name	Age	Weight in Kilograms	Nonprotein Nitrogen	Urea Nitrogen	Sugar	Uric Acid	Creatinin
1	H. R.	24	70.0	30	13	104	2.0	1.4
2	J. K.	19	61.4	30	13	110	1.9	1.3
3	W. B.	21	61.4	26	13	110	1.8	1.4
4	H. B.	25	61.4	31	15	93	2.2	1.5
5	A. K.	30	80.4	34	17	109	3.5	1.4
6	B. F.	23	61.8	27	13	120	1.9	1.6
7	J. S.	..	....	31	10	66	3.1	1.3
8	J. T.	35	70.0	36	18	107	3.4	1.0
9	J. H.	22	66.8	35	12	101	2.3	1.5
10	Miss W.	22	56.4	35	10	96	2.8	1.1
11	Miss M.	15	59.1	36	14	99	2.8	
12	Miss B.	18	57.7	35	13	105	3.2	
13	Mrs. J.	36	56.8	31	14	100	1.8	1.3
14	Miss R.	25	54.5	37	16	103	3.1	1.5
15	Miss K.	..	....	38	18	110	3.0	1.2
16	J. M.	22	66.0	33	13	96	2.9	1.1
17	Miss S.	32	....	37	18	102	1.3	1.3

* Seventeen cases between the ages 18 to 35; average uric acid, 2.5 mg.

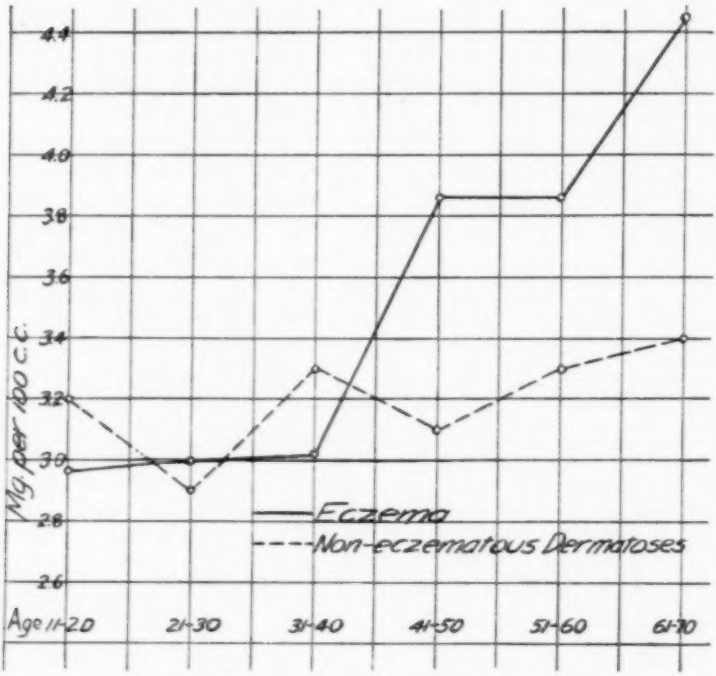
cent., had 4 mg. or more. Eighteen patients, or 11 per cent., had 5 mg. or more, and seven patients, or 4.6 per cent., had 6 mg. or more.

Of 164 patients, ninety had eczema; and of these sixty, or 66.6 per cent., had over 3 mg. of uric acid per 100 c.c. of blood. Thirty-five patients, or 39 per cent., had 4 mg. or more of uric acid; fifteen patients, or 16.6 per cent., had 5 mg. or more, and six patients, or 6.6 per cent., had 6 mg. or more.

It is thus seen that the incidence of hyperuricemia is higher in eczema than in other dermatoses. If it should be held that 3.5 mg. of uric acid is within normal limits, then computation discloses that 45, or 50 per cent., of the patients had a higher uric acid content than this amount.

EFFECT OF AGE ON URIC ACID CONTENT IN BLOOD

There can be no doubt that age has an important influence on the amount of uric acid in the blood.



Effect of age on uric acid content of blood.

Ninety-five cases of eczema and eczematoid conditions were studied. If these are classified according to age decades, it is seen that there is a gradually rising incidence in the uric acid figures (Tables 3, 4 and 5) from 20 up to 70 years. If we compare the noneczematous dermatoses with the cases of eczema, a striking contrast in the curve is seen. The average of the various age decades comes close to normal figures and does not exhibit any rising curve.

In the group designated eczema are unquestionably included a considerable number of cases which are eczematoid in nature, but doubt

TABLE 3.—*Age Incidence in Eczema* *

11-20	21-30	31-40	41-50	51-60	61-70	71-80
2.0	5.4	3.3	2.2	3.3	4.4	3.3
4.6	2.7	3.3	3.9	4.8	5.8	2.2
3.1	2.8	5.5	2.9	2.7	5.6	4.3
2.4	2.4	3.3	2.4	4.7	4.0	3.5
2.1	2.2	1.8	4.1	3.8	3.2	
2.9	4.0	2.2	5.3	3.8	3 9	
3.7	2.1	3.6	6.4	2.4	2.6	
	2.8	2.8	3.6	2.5	3.9	
		3.9	4.8	3.4	6.2	
		2.9	3.1	3.6	5.0	
		4.3	4.9	3.1	4.8	
		2.6	3.4	4.2	6.2	
		2.7	2.4	1.6	2.3	
		3.4	2.3	5.2		
		3.2	3.1	6.3		
			4.5	3.5		
			2.2	5.1		
			4.9	2.9		
			4.0	3.4		
			4.9	2.8		
			4.0	6.3		
			4.1	3.9		
			5.9	2.6		
			3.0			
			4.3			
2.97	3.005	3.02	3.86	3.86	4.45	3.33

* Tables 3, 4 and 5 and the chart do not include the entire 200 cases studied; they were completed prior to a number of the later analyses.

TABLE 4.—*Dermatoses, Excluding Eczema, Age Decades*

11-20	21-30	31-40	41-50	51-60	61-70	71-80	81-90
2.5	2.3	2.3	2.3	3.5	3.3	4.7	1.8
4.4	2.8	3.2	2.8	2.7	2.1	4.7	
2.6	2.4	2.8	2.3	2.7	5.2		
	3.3	2.5	3.3	4.7	3.0		
	2.8	6.6	3.0	3.9			
	3.0	2.6	3.1	3.9			
	1.7	2.8	4.0	2.5			
	4.0	2.2	3.2	3.3			
	3.8	2.2	3.1	3.1			
	3.1	5.0	2.6	3.8			
	4.1	3.5	2.2	3.1			
		4.3	4.6	2.4			
		2.9	4.4	4.2			
		5.0	2.8	2.9			
		3.1	2.3	4.0			
		4.8	4.0				
		4.7	4.0				
		2.2	4.5				
3.2	3.03	3.48	3.25	3.38	3.4	4.7	1.8

TABLE 5.—*Effect of Age on Uric Acid Content of Blood*

Noneczematous			Eczema		
Age	Mg.	No. of Cases	Age	Mg.	No. of Cases
11-20	3.2	3	11-20	2.97	7
21-30	2.9	10	21-30	3.005	8
31-40	3.3	13	31-40	3.02	15
41-50	3.1	16	41-50	3.86	25
51-60	3.3	12	51-60	3.86	23
61-70	3.4	4	61-70	4.45	13
			71-80	3.33	4

exists as to whether they constitute cases of genuine eczema. In many of these cases there are normal blood uric acid values. We have included them in order not to be guilty of any manipulation of the statistics.

For the most part, young patients with eczema have a normal amount of uric acid but there are several notable exceptions to this statement.

Pruritus.—In several of our cases of generalized pruritus in young persons there have been high uric acid values in the blood; in one there were 5.4 mg. and in another 4.7 mg. These cases are of particular interest.

Psoriasis.—Most of the patients with psoriasis had normal uric acid figures. In a few persons past middle age, the figures were high; but we believe that this was due to the coexistence of a renal condition and that it did not bear any causative relation to the cutaneous disease. The average uric acid in fourteen cases of psoriasis was 3.2 mg. per 100 c.c. of blood. The average age of these patients was 46 years.

INFLUENCE OF SEX ON URIC ACID IN BLOOD IN THE CASES OF ECZEMA

The average blood uric acid for male patients with eczema in our series was 4.16 mg. per 100 c.c., and the average for the females was 3.08 mg.

The average age of all the males whose blood was analyzed by us was 49.8 years, and the average age of the females was 42.1 years. The difference in age is not sufficient to explain a difference of 25 per cent. in the uric acid content. Some other factor or factors must be invoked. The fact that men are bigger eaters and larger consumers of flesh foods and alcohol than women must, we believe, be taken into consideration. The average weight of men would also be greater than the average weight of women.

TYPE OF PATIENTS STUDIED

The persons studied were all private patients from the middle and higher walks of life. They were all ambulatory or office patients and sought medical advice primarily for some cutaneous disorder. They ranged in age from 14 to 85 years, but by far the largest number fell within the decades from 30 to 60 years. The blood was taken within two to three hours after a light breakfast.

The data already submitted indicate that there is a high incidence of hyperuricemia associated with the eczema. This is the particular finding that we desire to present. As to the interpretation of this hyperuricemia there may be differences of opinion. There can be no

doubt that some of the cases represent instances of interstitial nephritis. In cases in which the nonprotein nitrogen and the urea nitrogen are high, the high uric acid figure is readily explained. But there are many cases among those studied by us in which the nonprotein and urea nitrogen were clearly within normal limits.

Creatinin.—It is interesting to note that in not a single patient was the creatinin in excess of the normal figure. Indeed, it varied within narrow limits, between 1 and 1.9 mg. In a case of nephritis in which the analysis was made in another laboratory but included in our series, it was 2.8 mg.

The low creatinin values are to be explained on the basis that our patients were not sick in the ordinary sense of the word, and retention of creatinin occurs only in fairly well advanced nephritis.

TABLE 6.—*Average Amount of Uric Acid in Blood in Different Dermatoses*

	Number of Cases	Average Uric Acid per 100 C.c. of Blood, Mg.
Psoriasis	11	3.2
Pruritus (local and general)	11	3.2
Acne	3	3.0
Urticaria	4	3.08
Eczema	95	3.8

CASE 1.—K. B., aged 22, a flabby young man who was overweight, had suffered for three years with violent itching of the face and of the upper part of the torso, with secondary eczema induced in part by irresistible scratching. His sleep was greatly disturbed.

This patient had 5.4 mg. of uric acid per 100 c.c. of blood, with 30 mg. of nonprotein nitrogen and 13 mg. of urea nitrogen. The urine was free from albumin and casts and had a specific gravity of 1.030. The blood pressure was 130.

Under a dietary regimen eliminating foods containing purin, there was an immediate and remarkable improvement in the itching and the eruption.

CASE 2.—W. S., aged 17, who weighed 130 pounds (60 kg.), suffered from a vesiculosquamous eczema of the hands at various intervals for six years. Blood analysis revealed 4.6 mg. uric acid, 35 mg. nonprotein nitrogen and 18 mg. urea nitrogen. This was the most youthful patient in our series with a high uric acid content in the blood. The eruption disappeared in a short time.

CASE 3.—A. McL., aged 40, was supposedly suffering from a trinito-toluene dermatitis of the face and hands due to contact with this substance during the war. The entire face was red, swollen and weeping. The case proved utterly refractory to all types of local medicaments applied over a period of many months.

The blood showed the presence of 5.5 mg. of uric acid, 32 mg. of nonprotein nitrogen and 13 mg. of urea. The blood pressure was 135 mm. The specific gravity of the urine was 1.010; there were no albumin or casts.

The patient has been placed upon a proper dietary regimen and virtually cured.

CASE 4.—I. P. H., a man, aged 39 years, with a recurring, markedly itching eczema of the legs, had had generalized outbreaks during the last three summers. The blood analysis gave the following figures: uric acid, 4.3 mg.; nonprotein nitrogen, 36 mg.; urea nitrogen, 16 mg. The father, mother and grandfather had gout. The youngest of five children had eczema. On appropriate diet and local treatment, great improvement occurred.

CASE 5.—H. C. D., aged 41, had suffered for some years from an erythematopapular eczema involving the forehead. Despite various forms of treatment, including the use of the roentgen ray, recurrences have developed. Examination of the blood disclosed the following findings:

Uric acid, 4.8 mg.; nonprotein nitrogen, 33 mg.; urea nitrogen, 14 mg.

An appropriate diet has been outlined for the patient, and he is at present free from the eruption.

CASE 6.—J. E. F., aged 35, sought medical advice for persistent areas of exfoliative glossitis of five months' duration, presenting somewhat the appearance of the "geographic tongue." His general health was excellent. The Wassermann test was negative. Examination of the blood revealed the presence of 5 mg. of uric acid, 36 mg. of nonprotein nitrogen and 16 mg. of urea nitrogen. This is the only case of this character in which a blood analysis has been made by us. The etiology of this curious condition has been entirely obscure.

CASE 7.—Mrs. K. G. S., aged 44, had vesicular eczema on the hands and fingers and an erythematous eczema on the face. She had four or five attacks, the last of which occurred three years ago. She had had one child. The patient felt tired and "dragged" in the mornings. Blood analysis revealed: uric acid, 4 mg.; nonprotein nitrogen, 34 mg.; and urea, 13 mg. Rapid improvement occurred on a milk diet.

CASE 8.—L. S., a man, aged 43, had a vesicular eczema which began on the arms one year ago and which spread over the entire body. There was violent itching.

Urinalysis revealed: specific gravity, 1.018; a trace of albumin, no casts and numerous pus cells.

Blood examination revealed: uric acid, 4.1; urea, 16; nonprotein nitrogen, 31; sugar, 82. Under a low protein diet and rest, the eruption disappeared.

CASE 9.—J. S., aged 33, a man, had had generalized pruritus of the body for sixteen years. He weighed 168 pounds (76.2 kg.) He was in good health but nervous. Blood examination revealed: uric acid, 4.7 mg.; nonprotein nitrogen, 36 mg.; urea nitrogen, 16 mg.; sugar 4.7 mg.; chlorids, such as sodium chlorid, 497 mg.; urine examination: specific gravity, 1.029; no albumin or sugar. The blood pressure was 120.

CASE 10.—J. R., a man, aged 20, had eczema in infancy and was subject to asthma in early childhood. He now had severe eczema of the face, with marked excoriations. Various food allergens were tried, but the results were negative. The patient's general health apparently was excellent. Chemical blood analysis revealed: nonprotein nitrogen, 30; urea, 14 mg.; sugar, 100; uric acid, 4.1.

INCONSISTENCIES IN BLOOD AND URINARY FINDINGS

The nonprotein nitrogen and urea may be within perfectly normal limits and yet nephritis may be present. A few such cases may be cited.

CASE 11.—M. S., a woman, aged 25, had a disease which had been diagnosed as lupus erythematosus. She had had nephritis in 1918 and had been confined to a hospital for some months. Examination of the urine showed a specific gravity of 1.010, 16 per cent. by volume of albumin, and 50,000 hyaline casts to the ounce of urine. Severe and fatal nephritis occurs in certain cases of lupus erythematosus.

The blood findings were: uric acid, 4; nonprotein nitrogen, 35; urea, 16; sugar, 102.

It is here seen that although the patient has a nephritis, the only nitrogenous element in her blood that is abnormal is the uric acid.

CASE 12.—E. B., a man, aged 59, had recurrent erythematovesicular eczema on the face, arms and legs. He selected his food and ate moderately. The

urine showed a trace of albumin and hyaline casts. The blood findings were: uric acid, 2.4; nonprotein nitrogen, 36; urea, 16; sugar, 110.

Here the blood would indicate perfectly normal kidneys, and yet the urine would hardly support such a contention.

CASE 13.—W. L. B., a woman, aged 55, nine months ago developed an eczema which has now become a universal exfoliative dermatitis. She had albumin and casts in the urine, and suffered retinal hemorrhages. The blood pressure at one time was 200. The blood findings were: uric acid, 5.4; nonprotein nitrogen, 35; urea, 16; and sugar, 144.

The nonprotein nitrogen and urea were normal, but the uric acid was very high. This case emphasizes, as do many others, the fact that uric acid first accumulates in the blood as a result of damaged kidneys. At the present time, the blood pressure is 155, and there is no albumin or casts in urine.

Instead of finding urinary evidence of kidney disease with low urea and nonprotein nitrogen figures, the reverse situation may be encountered.

CASE 14.—M. W., a man, aged 42, had a disease diagnosed as recurrent vesicular eczema of the hands. The blood revealed: uric acid, 4.9; urea, 20; and nonprotein nitrogen, 46. Urine examination revealed: specific gravity 1.018; no albumin or casts.

It would seem probable that this patient had renal disease.

Other cases of a similar character might be quoted.

Apparently diet is an influencing factor in some cases in the causation of hyperuricemia. One of the highest uric acid figures that we have observed was in a meat dealer, aged 42, suffering from eczema, who was in the habit of eating from three to four pounds (1.3 to 1.8 kg.) of red meat a day. His blood showed: uric acid, 6.4; urea, 16; and nonprotein nitrogen, 40.

On the other hand, those who are small eaters and live largely on a nonflesh diet, quite commonly have low nitrogenous blood values. A thin woman, aged 85, very careful of her diet, had only 1.8 mg. uric acid in her blood.

DISCUSSION

A survey of the cases cited reveals the fact that a high percentage of persons suffering from certain dermatoses, particularly eczema, have a hyperuricemia.

The question of an etiologic relationship between the uric acid and the associated dermatoses is a pertinent one. Gout and the uric acid diathesis were for many years invoked as the causes of many disorders, including a variety of diseases of the skin. The incrimination of uric acid in the blood as a cause of eczema is commonly found in the older textbooks. Let us quote an excerpt from the work of an eminent English dermatologist writing nearly forty years ago. Tilbury Fox, in 1884, in his treatise on "Diseases of the Skin," says:

> All disorders which are connected with the excreta in the system and their circulation throughout the blood current may furnish the exciting cause of eczema. This is a clinical fact of great importance. Given the tendency to eczema then the transmission of uric acid to the capillaries of the skin will so far derange as to aggravate, certainly, and now and again excite an eczematous eruption. This is what is meant by gouty eczema. By securing the absence of uric acid from the circulation the eczema will often disappear and always be more amenable to treatment. The passage of uric acid through the cutaneous capillaries of an eczematous subject acts as much the part of an irritant as do some externals. A gouty state of the blood may, therefore, excite and modify

an eczema. Some cases as I now refer to sometimes exist off and on for years and are saturated with arsenic and mercurials but which are only relieved by recognizing the complicating item of the free production and circulation of uric acid, and instituting a regime calculated to arrest the continuance of these conditions.

Lyman, writing on gout in the "Twentieth Century Practice of Medicine," expresses the following: "From the remotest antiquity a connection between gout and certain cutaneous diseases has been remarked by all clinical observers who have seen much of disorders that are experienced by the wealthier classes of society." Furthermore, "Eczema is frequently witnessed among the children of gouty families."

Osler writes: "Garrod and others have called special attention to the frequent association of eczema with the gouty habit."

To be sure, what we call eczema is a conglomerate concept that includes many conditions of diverse genesis, which cannot be definitely differentiated on the basis of the cutaneous phenomena alone. It would constitute valuable information, if we could scientifically demonstrate some of the dominant causes of eczema. The present study suggests that hyperuricemia may be an etiologic factor in the production of many eczematous conditions and allied disorders.

We are persuaded to believe that the excess of uric acid in the blood in many of the cases bears a causative relation to the accompanying eczema or allied pruritic disorder, by reason of the frequency of the association of the two conditions among the patients studied by us. We are fortified in this belief by the fact that in our experience these cases have responded more favorably and more rapidly to treatment than in previous years when the etiologic factor suggested was not suspected and the patients were not placed on an appropriate dietary regimen.

What is the significance of the excess of uric acid in the blood found by us in so large a series of cases?

Leaving out of consideration leukemia and the terminal stage of pneumonia, there are two conditions in which a high blood uric acid occurs—gout and nephritis. Without the presence of arthritic manifestations (which were absent in nearly all of our cases) or tophi, it would be hazardous to assert the belief that we were dealing with cases of hemic gout. It is quite possible that a considerable proportion of the subjects were suffering from renal change. Some unquestionably were, but it would be startling to believe that one half of our patients with eczema—persons who were not "sick" in the ordinary acceptation of the term, and who in the main had no complaint except their cutaneous distress—were nephritic. There are, it must be said, a considerable number of cases in which not only the uric acid is pathologically high, but in which the urea and nonprotein nitrogen also are beyond normal limits. Some of these patients exhibit albumin and hyaline casts in the

urine, whereas others do not. These cases represent, we believe, beginning instances of chronic interstitial nephritis.

We have observed, however, other patients in whom the uric acid was high, but in whom the nonprotein nitrogen and urea nitrogen were within normal limits. What is to be said of the hyperuricemia in these cases? The urinalysis in the cases in which examination was made was normal. Brief histories of some of the cases are appended.

In a separate group must be included the cases classified in Table 8. In most of these cases, not only was the uric acid high, but the nonprotein nitrogen and urea were likewise suspiciously above normal limits. These patients in the main represented the age decades from 40 to 70, whereas the previous group contained subjects from 17 to 45 years of age.

TABLE 7.—*Findings in a Group of Younger Patients*

Name	Age	Uric Acid	Urea	Nonprotein Nitrogen	Blood Pressure	Diagnosis	Urine
K. B.	22	5.4	13	30	130	Eczema	Specific gravity 1.030; no albumin or casts
Miss B.	20	4.1	15	31	...	Intestinal toxemia	
L. S.	43	4.1	16	31	...	Eczema	
Mrs. K. S. G.	44	4.0	13	34	...	Eczema	
I. P. H.	39	4.3	16	36	...	Eczema	
A. S.	43	4.9	14	30	...	Eczema	
H. C. DuB.	41	4.8	14	33	...	Eczema	
J. R.	20	4.1	14	30	...	Eczema	
Wm. S.	17	4.6	18	35	...	Eczema	
J. E. F.	35	5.0	16	36	...	Glossitis	
D. H.	54	4.8	14	30	160	Eczema	
A. McL.	40	5.5	13	32	135	Eczema	
J. S.	40	4.3	18	36	...	Dermatitis herpetiformis	Specific gravity 1.010; no albumin or casts
S. H. H.	45	5.0	18	38	...	Eczema	

Despite the fact that some of the patients in Table 8 had negative urinary findings, they must be regarded as patients with potential renal dysfunction by reason of the nitrogenous blood values.

With respect to the younger group (Table 7) with high uric acid and low urea and nonprotein nitrogen, scientific conservatism would suggest caution as to any dogmatic interpretation of the hyperuricemia. One might assume that these patients had a gouty or uric acid diathesis; on the other hand, they might be suspected of having some degree of renal incapacity. In beginning disease of the kidney, uric acid is the first nitrogenous constituent to be held back, and, therefore, to accumulate in the blood. Later accentuation of renal structural damage would then lead to a decreased elimination of urea and nonprotein nitrogen. May both series of cases not represent merely fine gradations of nephritic change? Our knowledge of the nature of gout is still involved in obscurity. All observers admit that the kidneys play an

important rôle. Haig states that it is not excessive production of uric acid but faulty elimination which causes an accumulation.

Garrod expresses the same thought when he states that gout depends on a temporary or continuous decrease in the ability of the kidneys to excrete uric acid, by which an overcharging of the blood with this product takes place.

Is there in gout a specific incapacity of the kidneys to eliminate uric acid, independent of permanent structural damage?

An interesting commentary on this problem is the observation that in all cases of gout that come to necropsy, the kidneys are found diseased. On the other hand, the vast majority of cases of chronic

TABLE 8.—*Findings in Patients Between the Ages of 42 and 75*

Name	Age	Uric Acid	Urea	Non protein Nitrogen	Blood Pressure	Urine
D. A. P.	47	4.1	20	43	130	Specific gravity 1.012; no albumin or casts
C. B.	50	5.2	28	46	115	Specific gravity 1.024; no albumin or casts
Mr. A. W.	42	4.9	20	46	175	Specific gravity 1.018; no albumin or casts
H. W. H.	47	5.9	20	40	...	Specific gravity 1.019; no albumin or casts
Mrs. E. C.	66	5.8	15	34	185	Specific gravity 1.026; no albumin or casts
Mrs. B.	48	4.3	11	36	...	
J. K. Y.	60	4.7	15	31	...	
H. S. R.	62	4.5	18	37	...	
Mrs. B.	55	5.1	20	44	...	Specific gravity 1.011; trace of albumin; no casts
Dr. C.	47	4.5	19	42	...	Specific gravity 1.019; few hyaline casts; no albumin
C. S.	65	6.2	15	33	...	Specific gravity 1.012; no albumin or casts; previously had casts for 4 or 5 months
D. W. C.	60	4.2	15	40	...	
Mr. R.	75	4.3	13	28	...	
Mrs. G.	58	4.7	14	30	150	Specific gravity 1.021; trace of albumin; few hyaline casts
Mrs. J. M. S.	62	5.6	15	32	160	Specific gravity 1.011; no albumin or casts
Wm. K.	42	6.4	16	40	110	Specific gravity 1.032; trace of albumin; many hyaline casts

interstitial nephritis are unaccompanied by symptoms clinically recognizable as gout.

Bearing on the interpretation of our cases is the series of cases reported by Myers, Fine and Lough.[3]

These writers reported about thirty cases in which there were high uric acid values without a corresponding retention of urea and creatinin; nonprotein nitrogen was not determined. Their patients appear, however, to have been hospital cases suffering from other systemic or visceral disorders, whereas ours were patients "on their feet," and, with

3. Myers, V. C.; Fine, M. S., and Lough, W. G.: The Significance of the Uric Acid, Urea and Creatinin of the Blood in Nephritis, Int. Med. **17**:570 (April) 1916.

few exceptions, not aware that they were not well except for their cutaneous affections.

The uric acid values reported by the foregoing observers were higher than ours, but this may possibly be explained at least in part by a difference of technical methods employed. They state that the blood picture in early interstitial nephritis and in gout are strikingly similar, particularly as regards the increase in uric acid. They suggest that a retention of uric acid may be earlier evidence of renal impairment of an interstitial type than the classical tests of albuminuria and cylinduria.

As early interstitial nephritis and gout present blood findings which are almost similar, the question arises, What are the distinguishing features between the two?

Sir A. B. Garrod,[4] in a postscript to his paper, remarked that it was not his opinion that gout was entirely dependent on the power of the kidney for the excretion of uric acid; he did not think that any hypothesis could be advanced with safety. Von Noorden [5] quotes Garród to the effect that the primary cause of the uric acid retention in gout lies in the kidney. He further says:

> Levison and Luff showed in a very large series of postmortems in Denmark and England, that in cases of interstitial nephritis, uric acid deposits in the articular cartilages are frequently found, although the condition was not suspected during life. Stripped of all unnecessary detail, this means that the retention of uric acid in the blood and the remaining phenomena of gout are the results of primary disease of the kidney. In certain cases, both nephritis and gout are amenable to clinical diagnosis. In other cases, nephritis, and in still other cases the uric acid diathesis remain for a long time, perhaps even up to the end of life, clinically free from symptoms and unrecognized.

He adds:

> It appears that continuous overloading of the blood with uric acid (nephritis) does not necessarily lead to gout, and, moreover, that this overloading is not followed by uric acid deposition without the accession of another still unknown, specific gouty factor.

Folin,[2] commenting on increased uric acid in the blood in gout and in nephritis, says:

> The characteristic and extraordinary feature of pure gout is that in most cases only the uric acid is increased. Whether this peculiar fact is to be interpreted in terms of a highly selective activity and correspondingly selective deterioration of the kidneys, or whether it means that uric acid is more difficult to excrete than any other waste product, a possibility suggested by the high normal levels and the excessive variations in the uric acid content of normal bloods, is by no means clear; nor is it certain that either one of these two hypotheses can furnish an adequate explanation. In nephritis leading to true uremia there is a gradual accumulation of all the nitrogenous waste products,

4. Garrod, Sir. A. B.: Observations on Certain Pathological Conditions of the Blood and Urine in Gout, Rheumatism and Bright's Disease, Med. Chir. Trans. **31**:83, 1848.

5. Von Noorden: Metabolism and Practical Medicine, **3**:669, 1907.

except ammonia, and in such bloods there is no constant relationship between the increase in the uric acid and in that of the total nonprotein nitrogen. But, on the whole, one can say that the uric acid seldom, if ever, shows a greater percentage increase than does the total nitrogen; that the uric acid accumulation, on the contrary, is usually less pronounced. In other words, in cases of generally diminished kidney efficiency one finds no support for the idea that the uric acid retention represents any special difficulty in the process of excretion. The statement made is true at least for advanced cases of nitrogen retention. Whether it is also or equally true for the early stages representing moderate nitrogen retention is not certain. Myers, Krauss and others have drawn the conclusion that the retention and accumulation of the uric acid precedes and exceeds that of the nonprotein nitrogen in the early stages of kidney insufficiency.

Under the circumstances, we would leave the interpretation of the hyperuricemia found in the series of cutaneous diseases studied by us for others to elucidate. We content ourselves with the actual findings which we have presented. A more intensive investigation, which would include the study of the purin metabolism, careful and repeated urinary examinations, blood pressure determinations and renal function tests, would doubtless shed added illumination on the subject.

CHEMICAL METHODS EMPLOYED

All blood specimens, both normal and pathologic, were drawn from two to three hours after a light breakfast, and the entire analysis completed on the same day. We found sodium oxalate more advantageous than potassium oxalate as the anticoagulant, owing to its low solubility which precludes the possibility of a large excess of the salt interfering with the subsequent protein precipitation.

The methods of analysis were, generally, those elaborated in 1919 by Folin and Wu.[6]

To 15 c.c. of whole blood diluted with water to 120 c.c. in a graduated mixing cylinder, 15 c.c. of 10 per cent. sodium tungstate were added, and the liquid thoroughly mixed. Fifteen c.c. of two thirds of normal sulphuric acid were then introduced, the cylinder being constantly shaken to prevent any clumping of proteins due to excessive local acidity. After all the acid had been added, the mixture was shaken for a few minutes longer. With this procedure, filtration could be started at once, the filtrates being, invariably, water-clear and neutral to congo red. The importance of having a neutral filtrate from which to precipitate the silver urate as well as the necessity of adding the acid slowly and with constant agitation to prevent absorption of uric acid, has been emphasized by various investigators.[7]

Neither the urea nor the nonprotein nitrogen was determined by nesslerization. To the solutions of ammonium carbonate (obtained by

6. Folin, O., and Wu, H.: J. Biol. Chem. **38**:98, 1919.

7. Folin and Wu (footnote 6); Pucher, S. W.: J. Biol. Chem. **52**:317, 1922. Folin, O.: ibid., **54**:153, 1922.

the urease digestion) and ammonium sulphate (resulting from the acid digestion) were added 3 c.c. of 10 per cent. and 3 c.c. of 40 per cent. alkali, respectively, and the liberated ammonia aerated into 5 c.c. portions of 0.01 normal sulphuric acid. The nitrogen was then determined by titrating the excess of acid with 0.01 normal alkali, the indicator being methyl red containing some methylene blue as a background color. With this indicator, the titration is accurate within 1.5 mg. of normal per 100 c.c. of blood, since a distinct color change is produced with one drop of alkali or acid. Fresh standard acid and alkali solutions were prepared each month. The exact strength of the acid was calculated from the weight of the barium sulphate obtained from 100 c.c. portions of the acid which were drawn from the same buret used in the subsequent titrations. The alkali, stored in a paraffin lined bottle and protected against the action of carbon dioxid by soda lime, was titrated against the acid before each analysis, and its proper factor obtained. Blank determinations were made with each new lot of reagents.

The precautions necessary in obtaining a filtrate suitable for the uric acid determination have already been pointed out. In our analyses, Benedict's phosphate standard, freshly prepared every six weeks, was employed in preference to the sulphite standard of Folin and Wu, because the more intense blue colors, obtained in the absence of sulphite, permit more accurate colorimetric comparisons. Otherwise the directions outlined by Folin and Wu were strictly adhered to. During the course of our work, several papers were published[8] in which the authors expressed their doubt both as to the accuracy of the uric acid determination and the nonadsorption of uric acid during the precipitation of the proteins. We, therefore, carefully investigated the entire subject and obtained results[9] which show that no adsorption of uric acid takes place if the tungstic acid protein precipitation is carried out as stated above, and that the Folin and Wu procedure for the determination of uric acid yields accurate results.

As a further check on our technic, analyses of normal blood specimens were made throughout the course of the work.

All figures are the averages of at least two closely agreeing results.

Reagents.—Kahlbaum's urea and uric acid were used; all other chemicals were chemically pure.

Apparatus.—All comparisons were made in a 5 cm. Duboscq colorimeter, by diffused daylight, by the same operator. The latter also determined all zero corrections (maximum error $< \pm 0.8$ mm.). The two 50 c.c. burets used in the titrations were matched; all pipets were calibrated to deliver.

8. Pucher, S. W. (footnote 7); Benedict, S. R.: J. Biol. Chem. **51**:187, 1922.
9. Brown, H., and Raiziss, G. W.: J. Lab. & Clin. Med. **8**:129, 1922.

TABLE 9.—*Cases Analyzed*

	Name	Age	Sex	Diagnosis	Uric Acid	Non-protein Nitrogen	Urea	Sugar	Creatin
1	Mrs. B.	48	F	Eczema	4.3	36	11	106	1.2
2	Mrs. D.	66	F	Eczema	5.8	36	17	119	1.1
					6.2	44	21	113	1.8
3	A. B.	38	M	Eczema	3.2	43	17	99	1.3
					2.7	36	18	63	1.2
4	Miss R.	18	F	Eczema	3.7	34	19	107	1.1
5	R. W.	57	M	Eczema	6.3	47	21	80	1.7
6	L. S.	43	M	Eczema	4.1	31	16	82	1.7
7	Mr. H.	47	M	Eczema	5.9	40	20	132	1.4
				3 months later	4.9	36	17	110	
8	Mr. R.	62	M	Eczema	4.5	37	18	123	1.4
9	I. W.	55	F	Eczema	2.8	28	15	108	1.3
10	Mr. McH.	68	M	Eczema	4.8	46	15	90	1.5
11	Mrs. M.	52	F	Eczema	2.9	41	20	88	1.6
12	J. S. S.	56	M	Eczema	3.4	42	15	83	1.8
13	J. S. G.	44	F	Eczema	4.0	34	13	81	1.5
14	Mrs. B.	55	F	Eczema	5.1	44	20	95	1.6
15	Mr. F.	59	M	Eczema and gout	3.5	38	15	133	1.4
16	Mr. E.	50	M	Eczema	4.9	45	25	70	1.5
17	G. A. B.	35	F	Eczema	3.4	38	15	78	1.3
18	I. F.	49	M	Eczema	4.0	36	21	82	1.6
19	Mr. T.	36	M	Eczema	2.6	42	17	79	1.5
20	Mrs. K.	30	F	Eczema	2.1	35	15	108	1.5
21	Mr. H.	60	M	Eczema	6.3	43	21	114	1.5
22	Mr. B.	57	M	Eczema	1.6	39	19	108	1.5
23	Mr. P.	76	M	Eczema	3.5	40	21	104	1.4
24	D. L.	56	M	Eczema	5.2	52	26	80	1.7
25	Mr. W.	42½	M	Eczema	4.9	46	20	94	1.5
26	Miss J.	20	F	Eczema	2.9	46	20	96	1.9
27	Mrs. D.	22	F	Eczema	2.2	40	18	80	1.6
28	Mrs. K.	30	F	Eczema (acute)	4.0	46	21	85	1.4
29	Mrs. L.	41	F	Eczema	2.2	29	12	115	1.1
30	E. S. C.	47	M	Eczema	4.5	42	19	93	1.5
31	C. S.	65	M	Eczema	6.2	33	15	146	1.4
32	T. B. G.	70	M	Eczema	5.0	35	..	104	1.97
33	D. P.	16	F	Eczema	2.1	37	12	90	1.6
34	H. S. R.	61	M	Eczema	3.9	37	18	105	1.5
35	Mr. C.	60	M	Eczema	4.2	40	15	98	1.4
36	M. B. F.	53	F	Eczema	3.6	38	19	110	1.4
37	P. H.	39	M	Eczema	4.3	36	16	96	1.4
38	M. E. L.	61	F	Eczema	2.6	..	..	110	
39	T. R.	34	F	Eczema	2.9	36	15	102	1.2
40	J. H. D.	69	M	Eczema	3.9	40	19	105	1.4
41	B. H.	11	F	Eczema	2.4	32	14	98	1.1
42	C. K.	52	M	Eczema	3.4	36	15	118	1.4
43	J. G. S.	57	M	Eczema	2.5	39	19	121	1.5
44	S. B.	45	M	Eczema	3.1	30	14	96	
45	Mrs. B.	70	F	Eczema	3.2	38	20	273	1.7
46	J. M.	34	M	Eczema	3.9	38	17	100	1.3
47	P. R.	75	M	Eczema	4.3	28	13	104	1.1
48	E. C.	22	F	Eczema	2.4	35	14	90	1.1
49	Mrs. S.	45	F	Eczema	2.3	35	16	112	1.4
50	W. B.	67	M	Eczema	4.0	35	15	110	1.3
51	I. H.	33	M	Eczema	3.6	32	13	95	1.1
52	A. S.	43	M	Eczema	4.9	30	14	106	1.4
53	E. B.	59	M	Eczema	2.4	36	16	110	1.3
54	J. S.	45	M	Eczema	3.4	32	13	106	1.4
55	F. C. T.	48	F	Eczema	2.4	32	13	100	1.2
56	L. S. K.	49	M	Eczema	3.1	33	12	125	1.3
57	E. L. S.	54½	M	Eczema	3.8	35	14	110	1.4
58	R. E.	18	M	Eczema	3.1	29	11	90	1.1
59	J. H.	60	M	Eczema	3.8	37	18	94	1.3
60	H. C. DuB.	41	M	Eczema	4.8	33	14	90	1.2
61	J. B.	42	M	Eczema	3.6	34	15	98	1.2
62	D. A. P.	47	M	Eczema	4.1	43	20	90	1.4
63	C. B.	50	M	Eczema	5.3	46	28	92	1.8
64	B. B.	79	F	Eczema	2.2	39	20	103	1.3
65	Wm. K.	42	M	Eczema	6.4	40	16	86	1.5
66	Wm. S.	17	M	Eczema	4.6	35	18	95	1.4
67	E. C.	60	F	Eczema	5.9	34	15	128	1.4
68	F. G.	58	F	Eczema	4.7	30	14	96	1.2
69	J. M. S.	62	F	Eczema	5.6	32	15	130	1.3
70	A. I. R.	27	M	Eczema	2.8	30	13	108	1.4
71	Dr. L.	52	M	Eczema (mild)	2.7	54	15	102	1.5
72	P. S.	35	F	Eczema	1.8	39	14	103	1.1
73	D. H.	54	M	Eczema	4.8	30	14	112	1.3

TABLE 9.—*Cases Analyzed—(Continued)*

	Name	Age	Sex	Diagnosis	Uric Acid	Non-protein Nitrogen	Urea	Sugar	Creatin
74	L. K.	30	M	Eczema	2.7	36	18	100	1.3
75	H. W.	69	M	Eczema	4.4	39	20	96	1.5
76	K. B.	22	M	Eczema	5.4	30	13	108	1.2
77	T. B.	39	M	Eczema	3.3	40	19	88	1.2
78	Mrs. L.	42	F	Eczema	2.2	30	13	98	1.1
79	A. McL.	40	M	Eczema	5.5	32	13	101	1.3
80	M. E. S.	40	M	Eczema (mild)	3.3	41	21	102	1.5
81	E. L. B.	44	F	Eczema	3.9	30	14	110	1.3
82	H. T. D.	51	M	Eczema	3.3	38	16	106	1.4
83	T. D.	19	F	Eczema	2.0	32	13	106	1.1
84	H. T.	40	M	Eczema	3.3	40	19	118	1.4
85	E. M. A.	26	F	Eczema	2.0	28	12	110	1.2
86	Mrs. R.	43	F	Eczema	3.6	34	15	110	1.3
87	H. S.	47	F	Eczema (or dermatitis)	2.3	38	19	101	1.4
88	M. G.	23	F	Eczema	1.8	..	12		
89	S. H. H.	45	M	Eczema	5.0	38	18	100	1.5
90	J. J. M.	42	F	Eczema	2.4	32	14	102	
91	L. R.	1	F	Eczema (infantile)	2.0				
92	S. R.	32	F	Eczema	2.7	32	15	96	1.1
93	C. L.	45	F	Eczema	3.3	41	22	104	1.5
94	E. J. L.	67	M	Eczema (Jan., 1921)	2.9	53	23	47	2.8
				(Jan., 1922)	6.0	38	18	62	1.7
				(Jan., 1923)	4.1	30	14	98	
95	B. C.	47	F	Eczema	3.3	36	18	116	1.1
96	J. S.	42	F	Eczema	3.0	..	12		
97	M. S.	30	F	Eczema	3.3	41	22	110	1.5
98	H. J. H.	22	M	Eczema	3.0	36	18	100	
99	A. B.	38	M	Eczema and pruritus	4.0	35	17	102	
100	S. H.	18	F	Eczema	2.9	35	17	97	
101	J. P. K.	63	M	Eczema	4.6	38	19	104	
102	E. S.	14	F	Eczema	3.7	36	16		
103	M. H. S.	32	M	Eczema	4.0	40	21		
104	C. W.	22	M	Eczema	3.8	38	19	108	
105	H. S.	52	F	Eczema	3.1	38	19	96	
106	S. L. S.	67	M	Eczema	4.5	37	18	90	
107	H. M.	31	M	Eczema	5.4	44	23	100	
108	R. J. S.	59	F	Eczema	4.6	32	15	115	
109	M. S.	53	M	Eczema	3.7	34	16	109	
110	D. H. F.	36	M	Eczema	4.5	35	16	110	
111	Wm. R.	..	M	Eczema	3.6	35	17	102	
112	Miss M.	21	F	Eczema	2.0	..	14		
113	J. R.	20	M	Eczema	4.1	30	14	109	
114	F. B. G.	21	M	Eczema	2.9	31	13	92	
115	J. G. H.	40	M	Eczema	4.1	34	16	96	
116	B. F.	38	M	Eczema	3.5	32	16	67	
117	A. A.	65	M	Eczema (acute erythema)	2.3	34	16	97	
118	D. G.	52	M	Eczematoid dermatitis	2.6	35	12	102	1.4
119	Mrs. R.	61	F	Eczematoid dermatitis	2.3	35	11	112	1.1
120	E. C.	42	F	Eczematoid dermatitis	2.4	39	13	104	1.4
121	H. J.	45	F	Eczematoid dermatitis	2.9	28	13	100	1.1
122	Mrs. P.	48	F	Dermatitis	3.0	31	14	122	1.3
123	G. W. T.	30	M	Dermatitis herpetiformis	1.7	39	20	80	1.5
124	J. S.	40	M	Dermatitis herpetiformis	4.3	36	18	98	1.5
125	F. M.	70	F	Dermatitis seborrhoica	3.0	40	19	105	1.5
126	M. L. B.	54	F	Neurodermatitis	3.1	37	17	98	1.4
127	P. T.	31	F	Neurodermatitis	2.2	30	14	116	1.1
128	W. L. B.	55	F	Exfoliative dermatitis	5.4	35	16	144	1.4
129	N. D.	60	M	Psoriasis	2.7	27	13	113	1.3
130	A. O.	35	M	Psoriasis	3.2	25	11	182	1.6
131	L. J.	18	M	Psoriasis	2.5	26	9	65	0.9
132	M. G.	44	F	Psoriasis	2.3	27	9	88	1.0
					3.3	27	14	118	1.1
133	J. A. H.	29	M	Psoriasis	2.8	29	11	111	1.5
134	Mrs. H.	60	F	Psoriasis	4.5	33	16	90	1.4
					5.4	42	18	93	1.6
135	R. S. I.	55	F	Psoriasis	2.5	38	18	98	1.4
136	Mr. H.	63	M	Psoriasis	5.2	46	23	88	1.6
137	Mrs. W.	45	F	Psoriasis	3.2	39	14	100	1.5
138	M. D.	57	F	Psoriasis	3.8	38	18	100	1.2
139	C. M. C.	51	M	Psoriasis	3.1	31	13	160	1.2
140	P. R.	..	F	Psoriasis	2.2	32	11	102	
141	E. S.	..	M	Psoriasis	4.2	39	19	107	
142	O. C.	38	F	Psoriasis	3.1	30	13	114	
143	C. M. C.	51	M	Psoriasis	3.6	28	12	147	
144	J. K. Y.	60	M	Parapsoriasis	4.7	31	15	117	1.1
145	W. M.	85	F	Pruritus	1.8	25	14	110	1.4

TABLE 9.—*Cases Analyzed—(Continued)*

	Name	Age	Sex	Diagnosis	Uric Acid	Non-protein Nitrogen	Urea	Sugar	Creatin
146	W. H. W.	68	M	Pruritus	2.1	32	15	113	1.2
147	Mr. McC.	60	M	Pruritus	3.3	37	16	115	1.4
148	L. T.	37	F	Pruritus capitis	2.3	26	11	91	1.4
149	P. A.	35	M	Pruritus capitis	2.9	29	14	106	1.4
150	Mrs. R.	49	F	Pruritus ani	3.1	42	20	94	1.4
151	H. G.	38	M	Pruritus ani	6.6	42	21	90	1.5
152	Mr. L.	39	M	Pruritus ani	3.5	29	12	102	1.1
153	J. F. S.	52	M	Pruritus ani et hiemalis	3.1	31	10	66	1.3
					3.8	39	16	94	1.3
154	G. H. B.	51	F	Pruritus hiemalis	2.4	38	19	98	1.3
155	D. L.	78	M	Pruritus hiemalis	4.7	38	18	99	1.4
156	F. M.	30	F	Pruritus ani et vulvae	2 8	36	18	95	1.8
157	R. G.	46	F	Pruritus vulvae	2.3	29	13	94	
158	M. P. W.	42	F	Pruritus generalisata	4.0	37	15	82	1.1
159	F. S. L.	52	M	Pruritus generalisata	4.0	40	19	108	
160	J. S.	33	M	Pruritus generalisata	4.7	36	16	101	
161	Miss K.	24	F	Acne	3.3	34	11	71	1.4
162	I. B.	20	F	Acne	2.6	..	12	103	
163	F. H.	23	F	Acne	3.1	..	13	92	
164	W. S. B.	43	M	Acne rosacea	4.6	40	18	118	1.6
165	R. S.	30	F	Rosacea	2.4	36	10	121	1.0
166	L. B. S.	57	M	Rosacea pustulosa	2.7	46	12	123	1.3
167	B. K.	38	M	Urticaria	2.8	40	22	70	1 4
168	I. L.	57	M	Urticaria	3.9	33	19	91	1.5
169	Mrs. H.	48	F	Urticaria	2.6	44	19	97	1.4
170	Mr. W.	24	M	Uritcaria (acute)	3.0	29	11	110	1.1
171	A. B.	35	M	Defluv. capillorum	2.5	38	19	102	1.4
172	H. M.	35	F	Defluv. capillorum	2.2	28	10	110	1.4
173	Mr. K.	43	M	Alopecia premature	2.8	34	9	123	1.2
174	Mr. B.	61	M	Syphilis	2.8	36	16	116	1.5
					3.8	38	16	94	1.4
175	Mrs. L.	46	F	Syphilis	4.0	35	17	106	1.1
176	M. K.	48	M	Syphilis latens	4.4	35	18	98	1.2
177	M. S.	25	F	Lupus erythematosus	4.0	35	16	102	1.5
178	A. G.	21	F	Lupus erythematosus	3.8	38	19	95	
180	A. P.	23	M	Xanthoma	1.9	27	12	129	1.4
					2.0	31	11	134	1.3
181	Mrs. L.	44	F	Chloasma	2.3	32	9	108	1.2
182	Miss B.	20	F	Gastro-intestinal toxemia	4.4	31	13	76	1.4
183	E. M. S.	46	M	Keratosis of face	3.1	48	22	119	1.6
184	Mrs. O.	47	F	Prurigo nodularis	2.2	35	17	106	1.2
185	Mrs. C.	31	F	Gangrene of skin (acute)	2.6	38	17	109	1.4
186	J. E. F.	35	M	Glositis exfoliat. areata	5.0	30	16	110	1.4
187	Mr. F.	72	M	Acute erythematous eruption	3.3	20	15	100	1.1
188	Mr. S.	46	M	Ringworm (eczematoid)	2.8	33	15	102	1.1
189	J. H. E.	35	M	Neurodermatitis	2.8	31	13	126	1.4
190	Mrs. L.	55	F	Lingual hemorrhages	2.8	..	14		
191	Mr. J. B. D.	44	M	Folliculitis of neck	3 2	32	15	110	
192	B. S.	23	F	Fissured fingers	2.1	28	11		
193	M. F. W.	35	M	Psoriasis	4.8	38	19	97	
194	A. K.	..	F	Redness and scaling of face	5.2	30	11	101	
195	C. R.	48	M	Syphilis	4.0	32	15	106	
196	C. R.	46	F	Syphilis	4.5	47	25	102	
197	Dr. C.	34	M	Pruritus ani	5.0	30	13	107	
198	C. S. W.	27	M	Pruritus ani	4.1	37	18	103	
199	J. J. R.	46	F	Leukokeratosis of mouth	2.2	38	14	97	

URIC ACID IN BLOOD

Table 10 shows that the average amount of uric acid in the blood rises from that of the patients weighing between 40 and 49 kilograms progressively up to that of those weighing from 60 to 69 kilograms. A steady increase is noted up to 80 kilograms, but beyond this point no further rise takes place, there being a slight decline in groups of patients of greater weight than 80 kilograms. Although there is a drop in the uric acid content of the blood after the fourth group, the average uric acid value is still above normal limits. The average amount of uric acid in the first three weight groups, comprising a

number of cases including 128 patients, is 3.5 kg. which is perfectly normal. The average of the second group, comprising 115 cases, is 4.5, which is abnormal. It would appear, therefore, that there is a definite increase of uric acid with rise in weight, but that beyond 80 kilograms no further rise takes place. This study of 243 patients indicates in general that higher uric acid values are to be expected in heavy persons.

TABLE 10.—*Influence of the Weight of the Individual on Uric Acid in Blood*

No. of Cases	Weight of Patient in Kilograms	Average Uric Acid Mg. per 100 c.c. of Blood
8	40-49	2.78
48	50-59	2.83
72	60-69	3.22
66	70-79	4.36
41	80-89	3.75
8	90-99	4.01

SUMMARY AND CONCLUSIONS

1. In a chemical study of the blood of over 200 patients suffering from cutaneous diseases, great variations in the uric acid content were found.

2. Over one half of the patients had eczema, and in these an increase in uric acid beyond the maximal normal limit (3.5 mg.) was observed in 50 per cent. of the cases.

3. In some cases of pruritus, both general and local, there were likewise high uric acid figures.

4. Classifying the eczema patients in age decades, it is seen that there is a rising uric acid curve from the fortieth to the seventieth year. This is not evident in the noneczematous subjects.

5. The average uric acid content of the blood in the male subjects was about 25 per cent. higher than among the female patients. The average age of the males was about seven years more than the females.

6. The blood of young patients with eczema did not as a rule contain large amounts of uric acid, but there were some notable exceptions.

7. The cause of the hyperuricemia is a matter for further study; we incline to the view that is to be explained on the basis of renal dysfunction.

8. Patients with psoriasis, acne, urticaria and certain other cutaneous diseases have a lower average uric acid blood content than those suffering from eczema.

9. We believe the hyperuricemia to be etiologically related to eczema and to pruritus in a considerable percentage of the cases studied.

10. Appropriate dietary measures have made many of our patients much more rapidly amenable to treatment than patients previously treated without this therapeutic measure.

A CLINICAL METHOD FOR THE ESTIMATION OF PROTEIN IN URINE AND OTHER BODY FLUIDS *

MARIAN C. SHEVKY AND D. D. STAFFORD, M.A.
SAN FRANCISCO

For clinical purposes, none of the methods used in the estimation of protein in urine, plasma, serum, transudates or exudates are satisfactory. Kjeldahl determinations are accurate but require too much time. The various methods given in textbooks on clinical pathology are rapid, but they are also grossly inaccurate. There seems, therefore, to be justification for the description of a centrifuge method which has been used in this laboratory for some time, since it combines simplicity with a considerably greater degree of reliability than any of the clinical methods possess.

The first step in the method is to test the protein containing fluid with heat and acetic acid. If more than a "moderate cloud" is obtained, the fluid should be diluted. This is necessary because the volume of

TABLE 1.—*Concentrations of Protein by the Kjeldahl and Authors' Methods*

Qualitative Test Heat and Acetic Acid	Protein Concentration Kjeldahl, Gm. per 100 C.c.	Volume of Protein Precipitated, C.c.
Moderate cloud	0.31	0.85
Light cloud	0.19	0.52
Slight cloud	0.12	0.34
Trace	0.05	0.17
Slight trace	0.03	0.12

precipitated protein should not exceed 1 c.c. after centrifuging. Since the term "moderate cloud" is vague, we give in Table 1 the concentrations of protein as determined by the Kjeldahl method and the corresponding volumes of protein obtained with our method, for what we call a moderate, light, and slight cloud, as well as the values for the concentrations described as "traces."

The next step is to pipet 8 c.c. of the fluid, diluted if necessary, into a 15 c.c. graduated centrifuge tube. Our experience has shown that the ordinary graduated tube is usually quite inaccurate, and we have used tubes which were recalibrated or have ourselves calibrated tubes with long narrow tips.

A layer of 5 c.c. of Tsuchiya's reagent is allowed to flow over the urine, a stopper inserted and the container slowly inverted three times. Tsuchiya's reagent contains 1.5 gm. of phosphotungstic acid and 5 c.c. of concentrated hydrochloric acid made up to 100 c.c., with 95 per cent. alcohol.

* From the Department of Medicine of Stanford University Medical School.

Exactly one minute after mixing it is centrifuged for fifteen minutes at 1,800 revolutions per minute. The fluid should be at a temperature of approximately 20 C.

Under these conditions, each 0.1 c.c. of precipitated protein is equivalent to 0.036 gm. of protein per 100 c.c. of fluid.

The actual concentration of protein in 30 specimens of urine were determined by the Kjeldahl method. Widely different concentrations were found, varying from 0.063 gm. per 100 c.c. to 3.01 gm. per 100 c.c. At the same time, protein determinations were made with our method

TABLE 2.—*Actual Protein Concentration as Determined by Kjeldahl and the Results of Determinations Using the Authors', Purdy's, Strzyzowski's, Esbach's and Tsuchiya's Methods*

Number	Actual Protein Concentration by Kjeldahl Gm. per 100 C.c.	Estimated Concentration Protein, Gm. per 100 C.c.				
		Author's Method	Purdy's Method	Strzyzowski's Method	Esbach's Method	Tsuchiya's Method
10	0.063	0.068	0.035	0.042	0.060	0.110
15	0.101	0.108	0.075	0.085	0.080	0.210
9	0.154	0.161	0.102	0.098	0.125	0.200
11	0.166	0.168	0.091	0.116	0.140	0.300
4	0.171	0.157	0.064	0.060	0.075	0.500
5	0.206	0.256	0.105	0.144	0.110	0.280
8	0.213	0.173	.....	0.126	0.130	0.240
23	0.221	0.236	0.089	0.135	.....	2.15
6	0.242	0.271	0.126	0.267	0.280	0.360
14	0.242	0.212	0.094	0.144	0.165	0.450
7	0.282	0.295	0.113	0.178	0.250	0.375
12	0.287	0.330	0.174	0.366	0.210	0.500
1	0.288	0.321	0.130	.....	0.265	0.490
2	0.404	0.374	0.192	.....	0.270	0.510
30	0.448	0.396	0.279	0.314	0.210	2.95
17	0.668	0.706	0.410	0.322	0.570	1.20
26	0.675	0.652	0.470	0.476	0.830	1.05
27	0.691	0.720	0.953	0.476	0.500	1.20
25	1.05	1.238	0.656	0.825	1.25	1.62
3	1.08	1.045	0.153	.....	1.750	0.155
13	1.15	1.17	0.462	0.880	1.02	2.10
29	1.42	1.52	0.523	0.298	1.30	1.75
22	1.48	1.62	1.08	0.140	2.05	5.20
20	1.77	1.83	0 063	0.161	1.70	3.05
16	2.01	1.94	0.855	3.500	1.85	4.10
24	2.01	2.23	1.28	1.700	1.70	3.60
18	2.34	2.30	1.07	2.800	1.75	3.30
19	2.43	2.30	0.212	0 212	1.60	4.10
21	2.89	2.41	2.03	0.199	2.05	4.50
28	3.01	3.10	1.27	1.270	2.55	6.50

and by the clinical methods described by Purdy,[1] Strzyzowski,[2] Esbach [3] and Tsuchiya.[4] These comparisons are given in Table 2.

It will be noted that it is only our method which gives approximately accurate results. In all the others, except Esbach's, there is a considerable constant error, and in all without exception the variable error is larger than in ours. The average percentage error with our method in these thirty determinations is 8.4 per cent. with a standard

1. Purdy: New York M. J. **69**:844, 1899.
2. Strzyzowski: Ztschr. f. Physiol. Chem. **88**:25, 1913.
3. Esbach: Bull. de therap. **98**:497, 1880.
4. Tsuchiya: Zentralbl. f. Med. **29**:105, 1898.

deviation of ± 9.7 per cent. In any series of determinations, 50 per cent. should give results which are within ± 6.5 per cent. of the true value.

The conditions we have selected are, of course, arbitrary, and there is no reason why they should not be altered if they are found inconvenient, so long as a new factor is found by comparison with Kjeldahl results. The time of centrifuging could not be shortened without some, though not a considerable, loss of accuracy. If a speed of 1,800 revolutions per minute cannot be obtained, any constant speed between 1,400

TABLE 3.—*The Effect of Varying Speed of Centrifuging on the Volume of the Protein Precipitate*

Revolutions per Minute	Number of Observations	Average Volume of Precipitate, C.c.
1,400	52	0.495
1,800	50	0.434
2,100	45	0.355
2,300	47	0.301

TABLE 4.—*The Effect of Varying Specific Gravity on the Volume of the Protein Precipitate; Time of Centrifuging, Seven Minutes*

Specific Gravity	Revolutions per Minute	Number of Observations	Average Volume of Precipitate, C.c.
1.005	1,800	4	0.322
1.040	1,800	4	0.318
1.005	2,100	4	0.266
1.040	2,100	4	0.269
1.005	2,300	4	0.254
1.040	2,300	4	0.251

TABLE 5.—*Effect of Varying the Length of Time Elapsing Between Adding Tsuchiya's Solution and the Commencement of Centrifuging; Time of Centrifuging, Seven Minutes*

Time in Minutes	Number of Observations	Average Volume of Precipitate, C.c.
1	8	0.32
2	8	0.33
3	8	0.33
4	8	0.34

and 2,300 revolutions per minute can be chosen and a correction made from the data given in Table 3.

The specific gravity of the fluid containing the protein appears to have no appreciable effect on the volume of the precipitate. The variation in specific gravity was obtained by adding salt to albuminous urine (Table 4).

The time elapsing between the mixing of the fluid and the Tsuchiya's reagent must be kept approximately constant, for it appears that the greater the delay the greater is the volume occupied by the precipitate. Data on this point are given in Table 5.

The only other important variable is the temperature. We have, however, not been able to determine the effect of temperature variations, because when the temperature of an albuminous urine, for instance, is raised or lowered it returns toward room temperature during the centrifuging, so that the degree of temperature which affects the results could be determined exactly only by centrifuging in a room of the required temperature. In the laboratory where the method was developed the room temperature during the day was seldom lower than 18 C. or more than 22 C., and within this range temperature variations do not seem to have any appreciable effect.

STUDIES OF DIABETES MELLITUS

II. RESULTS OF TREATMENT BY DIET ADJUSTMENT WITH REFERENCE TO MAINTENANCE REQUIREMENT AND THE KETOGENIC-ANTIKETOGENIC BALANCE *

WILLIAM S. McCANN, M.D.; R. R. HANNON, M.D.; WILLIAM A. PERLZWEIG, PH.D., AND EDNA H. TOMPKINS, A.B.

BALTIMORE

During the years 1921 and 1922 there were two highly important developments of knowledge which promise to be of epoch-making significance in the therapy of diabetes mellitus. The first of these is the regulation of ketogenesis. The second is the specific therapy by means of an extract of the pancreas discovered by Banting.[1]

The problem of treatment of diabetes mellitus has long been in a highly unsatisfactory state. Faced with a disease, which he could not cure, the clinician sought to prolong life by the methods of starvation and undernutrition brought into vogue by Allen,[2] and endorsed by Joslin.[3] Diets were frequently given which furnished adequate amounts of protein, but they were low in carbohydrate content, and generally contained relatively small amounts of fat because of the fear of inducing ketosis by excessive fat ingestion. It seemed generally to have been overlooked that the oxidation of fat continued during starvation and during the use of submaintenance diets, as well as the probability that body fat was capable of giving rise to ketone bodies to the same extent as an equal amount of ingested fat.

A most important contribution was made by Newburgh and Marsh [4] when they called attention to the successful use of high fat diets in the therapy of diabetes. At the time of the introduction of this method, it was generally considered to be a daring procedure. It was shown, however, that ketonuria ceased under the high fat regimen. It became apparent that the amount of fat ingested had little to do with ketogenesis, but that this is influenced by other factors, such as high protein feeding. In their practice, Newburgh and Marsh keep the protein

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* The Medical Clinic, Johns Hopkins Hospital.

1. Banting; Best; Collip, Campbell and Fletcher: Pancreas Extract in the Treatment of Diabetes Mellitus, Canad. M. A. J. **12**:141, 1922.

2. Allen, F. M.; Stillman, E., and Fitz, R.: Total Dietary Regulation in the Treatment of Diabetes. Monographs of the Rockefeller Institute for Medical Research, No. 11, New York, Rockefeller Institute for Medical Research, Publication Dept.

3. Joslin, E. P.: The Treatment of Diabetes Mellitus, Philadelphia, Lea & Febiger, 1917.

4. Newburgh, L. H., and Marsh, P. L.: The use of a High Fat Diet in the Treatment of Diabetes Mellitus, Arch. Int. Med. **26**:647 (Dec.) 1920.

intake of their patients low. They emphasize the necessity of lowering the level of protein metabolism. More recently, Marsh and Waller [5] showed that the lipemia of diabetes could be diminished in patients who were treated with such diets, and that great increases in fat ingestion were not accompanied by an increase in blood fat.

Up to this time clinicians knew little of the exact quantitative relationships in the meabolism of these substances which are ketogenic to those which are antiketogenic. In a rough way it was realized that "fat burned in the fire of the carbohydrates." In 1914, a most important study was made by Zeller,[6] who maintained a man at a minimal protein metabolism, but varied the proportions of fat and carbohydrate ingested over wide limits. He found that when only one molecule of monosaccharid was present for two molecules of fat in the diet, acetone appeared in the urine. The difficulty in accepting Zeller's results as final lies in the fact that he had no way of measuring the proportions of fat and carbohydrate actually metabolized, and that sources of antiketogenic substances other than carbohydrate were not considered. Nevertheless, Zeller's work marked a definite advance. A similar study made by Ladd and Palmer [7] yielded results agreeing in general with those of Zeller.

Highly important studies of antiketogenesis were carried out by Shaffer,[8] who demonstrated that the oxidation of aceto-acetic acid in alkaline solution by hydrogen peroxid in vitro was greatly accelerated by the simultaneous oxidation of glucose, fructose or glycerol. Shaffer [9] devised a trial method for the calculation of the molecular amounts of ketogenic and antiketogenic substances that might be derived from protein, fat and carbohydrate. This trial method, when applied to data in the literature of starvation experiments, of the Eskimo dietary, and of diabetic acidosis, yielded results which indicated that the minimum molecular ratio of ketogenic to antiketogenic substances for the avoidance of ketonuria in different human subjects was 1:1. A further confirmation of these findings was made by Shaffer [10] by a comparison of the total respiratory quotients with the degree of ketonuria of fasting men and diabetic subjects. He found that a molecular ratio

5. Marsh, P. L., and Waller, H. G.: The Relation Between Ingested Fat and the Lipemia of Diabetes Mellitus, Arch. Int. Med. **31**:63 (Jan.) 1923.

6. Zeller: Arch. f. Physiol. 1914, p. 213.

7. Ladd and Palmer: Carbohydrate Fat Ratio in Relation to the Production of Ketone Bodies in Diabetes Mellitus, Proc. Soc. Exper. Biol. Med. **18**:109, 1921.

8. Shaffer, P. A.: Antiketogenesis. I. An in Vitro Analogy, J. Biol. Chem. **47**:433 (July) 1921.

9. Shaffer, P. A.: Antiketogenesis. II. The Ketogenic Antiketogenic Balance in Man, J. Biol. Chem. **47**:449 (July) 1921.

10. Shaffer, P. A.: Antiketogenesis. III. Calculation of the Ketogenic Balance from the Respiratory Quotients, J. Biol. Chem. **40**:143 (Nov.) 1921.

of ketogenic to antiketogenic substances of 1:1 corresponded to a respiratory quotient of 0.76. His analysis of data from various sources indicated that when quotients are higher than 0.76, the catabolism of antiketogenic substances is great enough to remove aceto-acetic acid as fast as it is formed.

More recently, Shaffer [11] has shown that while the 1:1 ratio usually exists at the threshold of ketonuria, when excessive ketogenesis occurs, the amounts of ketone bodies excreted do not correspond with the amount expected if the 1:1 ratio were maintained, but can be explained better if one assumes in such cases the existence of a ratio of two molecules of ketogenic to one molecule of antiketogenic substances. He has, furthermore, tentatively modified somewhat the factors for estimating the molecular amounts of the two classes of substances arising from protein, fat and carbohydrate. With these modified factors, he obtained much better agreement between the predicted and observed excretion of ketone bodies in cases of excessive ketonuria.

Following the appearance of Shaffer's first work, a clear rational statement of the object and method of diet adjustment in diabetes was given by Woodyatt.[12] According to this author, the purpose is to bring the quantity of glucose entering the metabolism from all sources below the quantity which can be utilized without abnormal waste, and to adjust the supply of fat in relation to the quantity of glucose so that freedom from ketonuria may be attained. He proposed a method of combining foodstuffs of a diet in such proportions that for every molecule of diacetic acid which might arise from the foodstuffs of the diet, there should be available from the same sources one molecule of glucose or its equivalent of substances capable of being converted into glucose. These conditions are fulfilled when the foodstuffs are combined in the following proportions:

Fat grams $= 2 \times$ carbohydrate grams plus $\frac{1}{2}$ protein grams. He described the beneficial results of the use of such a diet in one patient with severe diabetes. From the report of this case, however, it is not possible to determine what actually occurred in the patient's metabolism because the urine nitrogen and the basal heat production were not determined.

The method of diet adjustment advocated by Woodyatt seemed so rational that it was introduced into the practice of this medical clinic. It was felt from the outset that it was highly essential to base all cal-

11. Shaffer, P. A.: Antiketogenesis. IV. The Ketogenic Antiketogenic Balance in Man and Its Significance in Diabetes, J. Biol. Chem. **54**:399 (Oct.) 1922.

12. Woodyatt, R. T.: The Object and Methods of Diet Adjustment in Diabetes Mellitus, Arch. Int. Med. **28**:125 (July) 1921.

culations on the actual metabolism of the patient as estimated from the data furnished by the basal heat production, urinary nitrogen excretion and the carbohydrate balance. The aim in every case was to furnish a diet which would cover at least the basal energy requirement, with the foodstuffs combined in the proportions advocated by Woodyatt. It was realized that the proportions of foodstuffs actually metabolized would probably be quite different from those of the diet at first, but the

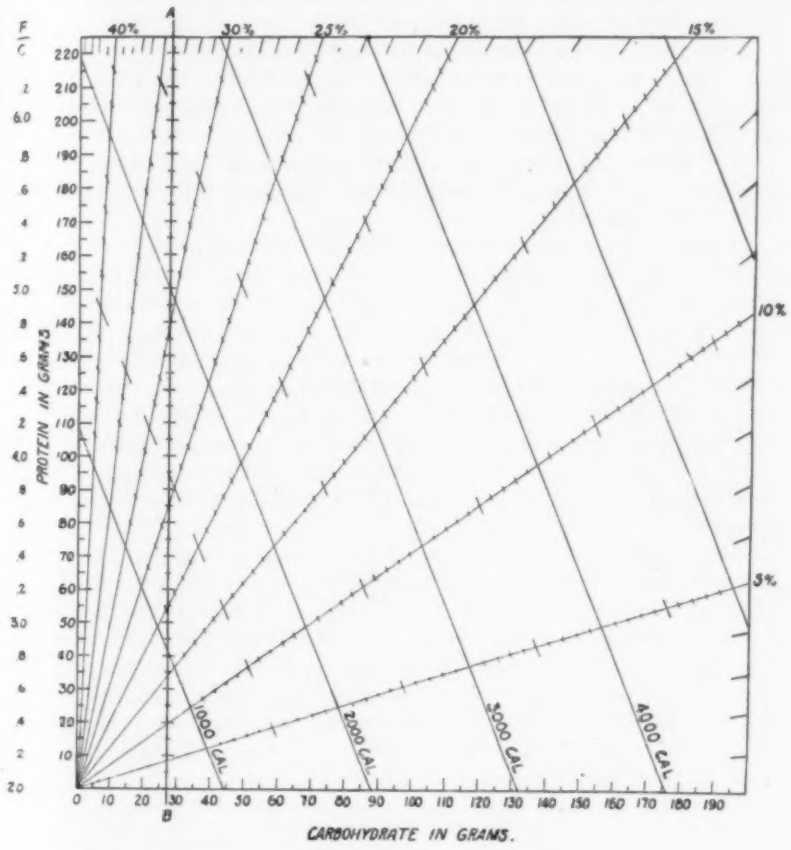

Chart 1.—To calculate a diet formula, select the diagonal line representing the number of calories required; choose the radial line corresponding to the percentage of the total calories to be furnished by protein; from the intersection of these two lines read off the amounts of protein and carbohydrate on the axes; the intersection of the *AB* with the radial percentage line determines the factor F/C. This factor multiplied by the number of grams of carbohydrate equals the grams of fat required.

hope was that the metabolism would gradually adapt itself to these proportions. Certain variations from Woodyatt's procedure were introduced, namely, in regard to the protein of the diet. This, it was felt, should be kept low in order to facilitate the diminution of the patient's protein metabolism. After reaching a minimal protein metabolism, the protein of the diet was increased to cover the requirement. This general plan of treatment was outlined in a previous communication,[13] together with a chart for the rapid calculation of the diet formula. This chart has been so useful that it has been reproduced in Figure 1.

The equimolecular ratio of ketogenic to antiketogenic substances was adhered to in spite of the later work of Shaffer [11] and others, which tended to show that this ratio furnished more carbohydrate than was necessary for the avoidance of ketone formation. As Shaffer himself pointed out, the molecular ratio is almost always 1 : 1 at the threshold of ketonuria, and this ratio is certainly the only safe minimum for clinical use.

Although the general plan of treatment was based on the idea of giving every patient at least enough food to cover the basal energy requirement (basal metabolism plus 10 per cent.), it was anticipated that a small percentage of patients would be unable to take this amount of energy in such diets without glycosuria. For such patients, some additional means of therapy, such as the use of insulin, is imperative.

Through the kindness of Dr. G. H. A. Clowes of the Eli Lilly Research Laboratories, it has been our privilege to study the effects of "insulin" (Iletin) on diabetic patients. One of the objects of this report on the dietotherapy alone is to afford some typical controls for a subsequent report of the use of dietotherapy plus insulin therapy.

During the year following the beginning of the present study, approximately 100 patients were treated in the manner to be described. Many of these patients were in general wards, especially in the female and negro wards, in which the most accurate excreta collections were impossible, and in which occasionally extra food was taken. The subjects of the present report were all studied in the white male ward of the medical clinic, which is equipped with a metabolism room with its own special diet kitchen. The observations of these patients were all made with the highest degree of accuracy.

METHODS OF STUDY

The management of the metabolism ward is essentially that described by Gephart and DuBois [14] for the ward of the Russell Sage Institute

13. Hannon, R. R., and McCann, William S.: A Graphic Method for the Calculation of Diabetic Diets in the Proper Ketogenic Antiketogenic Ratio, Johns Hopkins Hosp. Bull. **33**:128 (April) 1922.

14. Gephart, F. C., and DuBois, E. F.: The Organization of a Small Metabolism Ward, Arch. Int. Med. **15**:829 (May) 1915.

at Bellevue Hospital. Feces and urine collections, diet preparation and calculations were carried out in a manner identical with that described by these authors.

Nitrogen determinations on feces and urine were made by the Kjeldahl method. Phosphorus was determined gravimetrically by an official method.[15] Calcium determinations were made by McCrudden's method.[16] The urine sugar was usually determined by titration with Benedict's copper reagent. When present in amounts insufficient to give a qualitative test with copper reagents, the total urine sugar was determined by Benedict's colorimetric method.[17] In certain of the cases the total acetone bodies were determined by the method of Van Slyke and Cullen,[18] and reported as beta-hydroxybutyric acid. In other cases, the total organic acid excretion was measured by the method of Van Slyke and Palmer.[19] Except in well-marked ketonuria, the acetone bodies make up only a part of the total organic acids. Ammonia was determined by the method of Van Slyke and Cullen.[20]

The analyses of blood for sugar and carbon dioxid combining power were made on specimens collected before breakfast. The sugar of the whole blood was determined by the method of Folin and Wu.[21] For the determination of the alkaline reserve of the plasma, Van Slyke and Cullen's method was used.[22]

Many of the basal metabolism determinations were made in the course of respiration experiments with the Tissot spirometers, Loven valves and air analyzers, as described in a previous publication.[23] For other patients, the routine procedure was to determine the metabolism in a closed circuit apparatus,[24] equipped with a graphic recording

15. Official and Tentative Methods of Analysis of the Association of Official Agricultural Chemists, Washington, D. C., 1920, p. 2.

16. McCrudden, F. H.: The Determination of Calcium in the Urine, J. Biol. Chem. **10**:187, 1911-1912.

17. Benedict, S. R., and Osterberg, E.: A Method for the Determination of Sugar in Normal Urine, J. Biol. Chem. **48**:51, 1921.

18. Van Slyke, D. D., and Cullen, G. E.: Studies in Acidosis. VII. The Determination of Beta-Hydroxybutyric Acid, Acetoacetic Acid, and Acetone in the Urine, J. Biol. Chem. **32**:455, 1917.

19. Van Slyke, D. D., and Palmer, W. W.: Studies in Acidosis. XVI. The Titration of Organic Acids in the Urine, J. Biol. Chem. **41**:567, 1920.

20. Van Slyke, D. D., and Cullen, G. E.: A Permanent Preparation of Urease and Its Use in the Determination of Urea, J. Biol. Chem. **19**:211, 1914.

21. Folin, O., and Wu, H. A.: A Simplified and Improved Method for the Determination of the Sugar in the Blood, J. Biol. Chem. **41**:367, 1920.

22. Van Slyke, D. D., and Cullen, G. E.: The Bicarbonate Concentration of the Blood Plasma and a Method for Its Determination, J. Biol. Chem. **30**:289 and 347, 1917.

23. McCann, W. S., and Hannon, R. R.: Studies of Diabetes Mellitus. I. The Effect on the Respiratory Exchange of the Ingestion of Glucose, Glycerol Calcium, Hexose Phosphate, Calcium Glycerophosphate, Bull. Johns Hopkins Hosp. **34**:73 (March) 1923.

24. Metabolor, made by the Toledo Technical Appliance Co.

device so that the principle of Krogh [25] was used in the measurement of the oxygen consumed, assuming an average respiratory quotient of 0.72 in calculating heat production of diabetic subjects.

Calculations of the ketogenic-antiketogenic balance have been based on the actual metabolism of the patients, but only in cases in which the subjects were kept quietly in bed so that the heat production could be estimated (basal metabolism plus 10 per cent.). For this reason, the rule was made that patients showing ketonuria should be kept in bed as nearly at absolute rest as possible until the urine ceased to contain acetone. In calculating the foodstuffs metabolized, the following procedure was followed:

Urine Nitrogen grams $\times$ 6.25 = Protein metabolized, gm. P. C., carbohydrate utilized = Food carbohydrate minus urine sugar. Fat oxidized, grams = $\frac{\text{Total heat produced} - 4.1\ (P + C)}{9.3}$.

Total heat produced = Basal metabolism plus 10 per cent.

In the diet and metabolism tables the available diacetic acid, *FA*, and the available glucose, *G*, were calculated by the method of Woodyatt,[12] in accordance with the formulas:

$$FA = 0.9F + 0.46P$$
$$G = 0.1F + 0.58 + C$$

in which F = grams of fat, P = grams of protein, and C = grams of carbohydrate.

The diet and metabolism tables have been abbreviated by deleting relatively unimportant parts for the sake of space. The essential data from the complete tables is recorded graphically. All data relative to ketogenic-antiketogenic balance during periods of significant ketonuria have been retained in the tables.

REPORT OF CASES

CASE 1.—*History.*—W. A., a mechanic, aged 22 years, admitted to the hospital on Dec. 15, 1921, complaining of general weakness, had been in good health until October, 1921, when he noticed excessive thirst, hunger, frequent and excessive urination, general weakness and a loss of weight of 20 pounds (9.07 kg.) in two months. For three weeks before admission he had noticed that he was drowsy and that he tired easily. For two weeks he had suffered from a dry cough accompanied by a choking sensation. Drowsiness had increased very much in the two days prior to admission.

The family history was not important except for the fact that his father was very obese. The past history was unimportant. His best weight was 145 pounds (65.77 kg.). One year before admission, he weighed 140 pounds (63.5 kg.) and maintained this weight up to the onset of illness. His weight on admission was 102 pounds (46.26 kg.).

25. Krogh, A.: Respiration Apparatus for the Determination of the Energy Metabolism in Man, Wien. klin. Wchnschr. **35**:290, 1922.

TABLE 1.—*Diet and Metabolism in Case 1*

Date	Urine						Blood		Diet			Foodstuffs Metabolized						Food, Calories	Calories Required Estimated	Body Wt., Kg.	Surface Area, Sq. M.
	Volume, C.c.	Sugar, Gm.	Acetone	Diacetic Acid	Total Organic Acid, C.c. N/10	Nitrogen, Gm.	Carbon Dioxid, C P Volume, %	Sugar, %	Protein, Gm.	Fat, Gm.	Carbohydrate, Gm.	Protein, Gm.	Fat, Gm.	Carbohydrate, Gm.	Available G, Gm.	Available F A Gm.	F A / G				
12/15/21	....	++++	+++	+++	...	....	27.7	.....	....	...	....	...	...	....	..	...	..	.....	.....	....	....
12/16/21	2,900	56.3	++	++	...	18.6	27.1	0.351	....	...	....	111	126	—56	21	162	7.7	....	1,400	44.4	1.49
12/17/21	3,150	72.5	++	++	...	19.8	30.2	0.303	20.6	110	50.7	123	106	—22	60	152	2.6	1,314	.....	....	....
12/18/21	6,110	92.6	++	++	...	25.1	....	.....	20.8	112	50.2	157	109	—42	59	162	2.7	1,331	.....	....	....
12/19/21	5,170	106.5	++	++	...	20.2	37.4	0.272	20.4	111	51.6	125	120	—55	30	165	5.5	1,289	.....	....	....
12/20/21	5,870	97.8	++	++	...	18.2	....	.....	19.5	109	51.2	114	121	—47	31	161	5.2	1,307	.....	....	....
12/21/21	3,600	49.3	++	++	...	19.1	53.7	0.268	0	0	0	119	120	—49	32	163	5.1	0	.....	....	....
12/22/21	4,330	50.2	+	+	...	19.1	58.8	0.234	0	0	50.0	119	98	0	79	143	1.8	200	.....	....	....
12/23/21	5,090	28.0	+	+	...	15.9	....	.....	61.2	110	26.1	99	106	2	70	141	2.0	1,380	.....	....	....
12/24/21	5,950	119.0	+	+	...	14.9	65.5	0.356	60.2	109	40.4	93	?	?	..	...	...	1,424	.....	....	....
12/25/21	6,200	100.4	+	+	...	12.4	....	.....	17.5	111	51.8	78	?	?	..	...	...	1,312	.....	....	....
12/26/21	5,160	47.5	+	+	...	9.3	....	.....	15.2	110	52.2	58	133	5.3	52	146	2.8	1,400	.....	....	....
12/27/21	6,170	30.6	+	+	...	11.1	66.2	0.290	....	...	50.0	69	112	19.4	71	130	1.8	200	.....	45.8	....
12/28/21	4,820	25.4	+	+	...	10.6	....	.....	20.9	111	50.7	66	110	25.3	75	127	1.7	1,338	.....	....	....
12/29/21	6,100	44.0	+	0	...	15.4	....	.....	19.7	110	50.4	96	?	?	..	...	...	1,332	.....	....	....
12/30/21	5,720	10.4	+	0	...	10.5	....	.....	21.6	110	50.5	66	104	40.1	89	121	1.4	1,337	.....	....	....
12/31/21	4,360	35.1	+	+	...	8.2	.. .	0.158	19.7	110	51.4	51	121	16.3	58	130	2.2	1,311	.....	....	....
1/ 1/22	5,000	28.7	+	..	...	8.5	....	.....	20.2	110	49.3	53	118	20.6	63	128	2.0	1,304	.....	....	....
1/ 2/22	4,720	36.3	+	+	...	9.9	....	.....	41.5	115	46.3	62	119	10.0	58	133	2.3	1,429	.....	....	....
1/ 3/22	4,470	37.2	±	—	...	10.8	68.5	0.294	41.5	115	46.3	67	117	9.1	69	133	2.2	1,429	.....	....	....
1/ 4/22	4,080	32.5	—	—	634	11.9	.. .	.....	42.0	114	47.0	74	106	14.5	68	126	1.8	1,425	1,400	....	1.48
1/ 5/22	4,500	10.7	—	—	457	9.0	....	.....	41.0	116	46.5	55	110	35.8	79	122	1.5	1,434	.....	43.8	....
1/ 6/22	6,300	0	..	..	431	6.9	.. .	.....	17.4	2.6	44.1	43	112	44.1	80	119	1.5	276	.....	43.0	....
1/ 7/22	4,580	0	—	—	466	5.9	....	.....	12.9	1.8	38.2	37	117	38.2	71	121	1.7	178	.....	43.2	....
1/ 8/22	3,880	0	—	—	487	7.7	....	....	41.9	115	46.2	48	109	46.2	85	118	1.4	1,438	.....	44.8	....
1/ 9/22	3,560	0	—	—	527	6.1	59.3	0.156	41.6	116	46.7	38	118	43.4	77	122	1.6	1,428	.....	45.9	....
1/10/22	2,220	0	+	—	666	6.0	....	.....	49.5	121	46.8	38	127	43.5	78	131	1.7	1,515	1,430	46.2	1.51

Physical Examination.—Examination on Dec. 15, 1921, revealed a temperature of 97 F.; pulse rate, 94; respirations, 24; blood pressure: systolic, 115, diastolic, 78; height, 170 cm. The patient was a markedly emaciated young white man, lying quietly in bed and apparently very drowsy; the respiratory rate and amplitude were both increased. A fruity odor was noticeable. When aroused the patient was mentally clear but soon lapsed into drowsiness. The face was flushed and dry. The cheeks were sunken. The mucous membranes were red, the tongue beefy, dry and furrowed. The eyes were normal, except for low ocular tension. No other abnormalities were noted except a slight impairment of resonance and a few moist râles in the left upper side of the chest. This observation was not confirmed on subsequent examination. The urine showed the presence of a large amount of sugar, acetone and diacetic acid. The blood flowed sluggishly; it was rather thick and dark red. The carbon dioxid combining power of plasma was 27.7 volume per cent. There were 6,400,000 red blood cells, 18,000 white blood cells and 90 per cent hemoglobin. The Wassermann reaction was negative. The patient was starved and forced to take large aomunts of water.

December 16: The patient was less drowsy. The odor of acetone persisted. Evidence of desiccation was still marked. Starvation was continued. During this day the fluid intake exceeded the output by 3,000 c.c. The hyperpnea tended to diminish.

December 17: The patient was more alert in the morning. He was given 21 gm. of protein, 110 gm. of fat and 51 gm. of carbohydrate. The blood plasma taken in the morning showed the same low carbon dioxid combining power, and a marked hyperglycemia, 0.351 per cent. Further data are given on the metabolism chart.

December 18: Steady improvement was noted; the patient was brighter and more comfortable.

December 19: Hyperpnea and odor of acetone were much diminished. Roentgen-ray report: Chest: The lungs were clear.

December 24: The patient's condition was definitely improved.

January 4, 1922: The patient admitted having stolen food on one occasion, December 29. On January 5, he was admitted to the special metabolism ward.

Comment.—The course of the patient under treatment can best be followed by reference to the diet and metabolism chart in Table 1. Much of the data is recorded graphically in Chart 2.

The diet from December 16 to 20 furnished enough calories to cover the basal metabolism. In this period, the evidences of acidosis disappeared, the carbon dioxid capacity of the plasma increased, and hyperglycemia was somewhat less. Large amounts of sugar continued to be excreted.

In order to hasten the disappearance of glycosuria, the patient was starved again on December 21, and given only 1,000 gm. of 5 per cent. vegetables on December 22. This was partly effective in reducing both the blood sugar level and glycosuria.

On December 23 and 24, the diet furnished about 1,400 calories, of which 19 per cent. were derived from protein, fat and carbohydrate, being in the proportions of Woodyatt's formula. This was thought to be too much protein, because on the second day the blood sugar had increased, and glycosuria was greater.

On the twenty-fifth and twenty-sixth, the diet was again changed to give about 1,300 calories, with 5 per cent. derived from protein. This was followed by a decreased sugar elimination. On the twenty-seventh, only 1,000 gm. of green vegetables were given, and from the twenty-eigth to January 1 inclusive, the 1,300 calorie diet was resumed. During this period a break in diet was admitted.

From January 2 to 5 the amount of protein given was doubled. On the sixth and seventh the diet was low in protein, contained almost no fat, but

almost as much carbohydrate as before. At this time glycosuria ceased. Between January 8 and 15, it was possible to increase the calories to 1,500 gm. and the protein intake to 50 gm., without a return of glycosuria. This diet was continued up to January 30, with the exception of January 15, on which day green vegetables were given.

In Period I, from January 18 to 22, inclusive, stools were saved quantitatively, separation of feces being accomplished by means of carmine given with the breakfast of the first day of each period. Periods II, III, and IV began on January 23 and 28 and on February 2, respectively. Complete excreta collections were made for the purpose of determining the balance between the intake

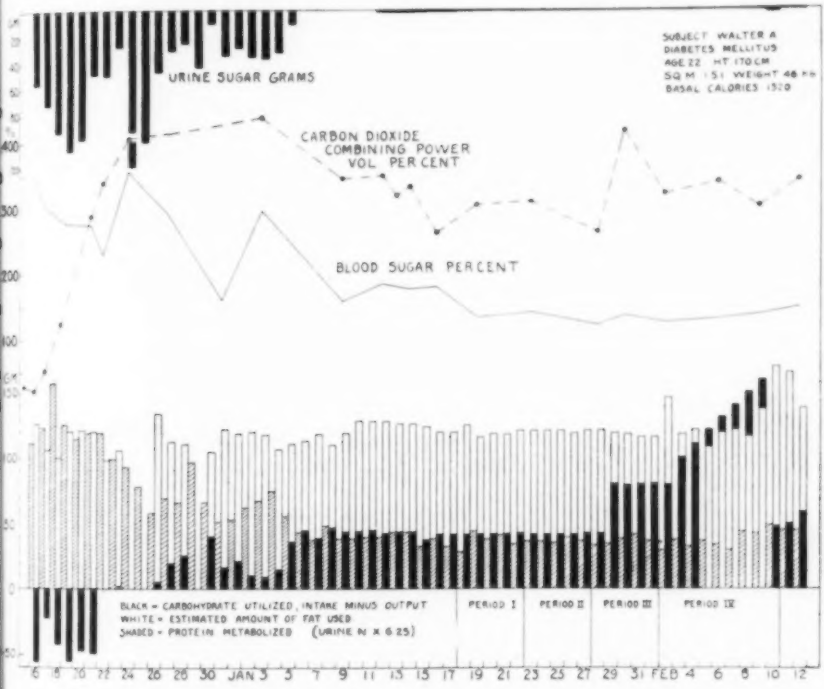

Chart 2 (Case 1).—Metabolism chart of Walter A. Black columns represent carbohydrate in grams utilized or excreted in the urine. The shaded columns represent protein metabolism in grams per diem. Unshaded columns represent the estimate of the amount of fat oxidized a day.

and outgo of calcium, phosphorus and nitrogen. These results will be discussed separately (Table 2).

During Period II, 60 gm. of calcium hexose phosphate were given daily. Though this increased the available carbohydrate by 37 gm., no increase in blood sugar or sugar excretion occurred.

During Period III, it was demonstrated that the patient could tolerate the addition of 37.5 gm. of glucose to the diet just as well. At the time it was thought that the accumulation of a large phosphorus balance during Period II

TABLE 2.—*Nitrogen, Phosphorus and Calcium Balances in Case 1*

Period	Dates Inclusive	Food N, Gm.	Urine N, Gm.	Feces N, Gm.	Total N Excreted, Gm.	N Balance, Gm.	Food P, Gm.	Added P, Gm.	Total P Intake, Gm.	Urine P, Gm.	Feces P, Gm.	Total P Excreted, Gm.	P Balance, Gm.	Food Ca, Gm.	Added Ca, Gm.	Total Ca Intake, Gm.	Urine Ca, Gm.	Feces Ca, Gm.	Total Ca Excreted, Gm.	Ca Balance, Gm.
I	Jan. 18-22	40.5	101.7	13.95	115.7	—75.2	13.08	0	13.08	4.15	8.15	12.30	+0.78	3.17	0	3.17	1.70	2.81	3.51	—0.34
II*	Jan. 23-27	40.5	63.6	17.27	80.9	—40.4	13.06	56.88	69.94	9.86	48.10	57.96	+11.98	3.17	71.67	74.84	1.55	58.39	59.94	+14.90
III	Jan. 28–Feb. 1	40.0	53.2	15.97	69.2	—29.2	13.03	0	13.03	3.75	10.42	14.17	—1.14	3.20	0	3.20	1.06	7.68	7.74	—4.58
IV	Feb. 2-11	75.2	80.4	35.44	115.8	—40.6	27.11	13.19	40.30	8.52	28.61	37.13	+3.17	7.28	17.14	24.42	1.99	24.91	26.90	—2.48

* Calcium hexose phosphate, 300 gm.

TABLE 3.—*Diet and Metabolism Data in Case 1, Second Admission*

Date	Urine						Blood		Diet Received			Foodstuffs Metabolized						Food, Calories	Calculated Requirement	Body Wt., Kg.	Surface Area, Sq. M.
	Volume, C.c.	Sugar, Gm.	Acetone	Diacetic Acid	B-oxybutyric Acid, Gm.	Total Nitrogen, Gm.	Carbon Dioxid, C P Vol. %	Sugar, %	Protein, Gm.	Fat, Gm.	Carbohydrate, Gm.	Protein, Gm.	Fat, Gm.	Carbohydrate, Gm.	Available F A, Gm.	Available G, Gm.	F A / G				
11/ 3/22	3,940	204.8	+++	++	.....	3.1	....	.....	....	....	....	....	....	....	....	....	....	.....	.....	....	....
11/ 4/22	2,380	90.0	+++	++	.....	11.9	47.5	0.237	39.7	128	56.4	74.5	132	—33.6	153	22.9	6.68	1,582	1,400	46.5	1.52
11/ 5/22	3,300	91.0	+++	++	.....	10.3	....	.....	39.9	129	55.0	64.0	137	—36.0	153	14.8	10.3	1,560	1,400	....	....
11/ 6/22	6,450	90.0	+++	++	38.25	9.9	28.1	0.256	41.9	131	53.5	61.5	138	—36.5	153	13.0	11.8	1,605	1,400	45.5	....
11/ 7/22*	6,450	54.0	++	+	23.82	9.5	29.6	0.235	7.8	144	10.8	59.4	127	—7.2	142	30.0	4.74	1,570	1,400	....	....
11/ 8/22*	4,400	31.0	++	+	13.03	6.1	31.5	0.231	7.8	144	10.8	37.8	125	15.8	130	50.2	2.59	1,570	1,400	43 3	....
11/ 9/22	3,420	20.0	++	+	5.23	4.3	34.7	0.234	10.4	88	37.9	26.6	130	17.9	129	46.2	2.79	994	1,400	42.1	....
11/10/22†	3,420	62.4	+	—	8.61	4.3	47.8	0.294	10.4	86	49.0	26.6	144	—13.4	142	16.3	8.71	1,042	1,400	....	....
11/11/22	3,540	51.0	+	—	2.09	6.5	....	.....	11.2	85	48.4	40.4	143	—2.6	147	35.1	4.19	1,035	1,400	42.7	1.48
11/12/22	3,750	37.5	+	—	2.00	5.4	....	.....	11.4	86	49.1	33.8	129	11.6	132	43.7	3.04	1,046	1,400	45.0	....
11/13/22	3,900	33.5	+	—	2.35	5.3	....	.....	11.2	85	48.6	33.1	128	15.1	130	47.1	2.76	1,036	1,400	46.0	....
11/14/22	3,500	22.5	+	—	0.69	4.6	....	.....	11.3	86	48.7	28.5	127	23.2	127	52.4	2.42	1,041	1,400	46 0	....
11/15/22	3,520	14.4	+	—	....	4.4	....	0.242	12.0	86	48.4	27.6	122	24.0	123	62.2	1.98	1,042	1,400	48.0	1.50
11/16/22	3,840	11.5	..	..	....	4.7	....	.....	11.4	86	48.0	29.2	120	36.5	121	65.4	1.85	1,040	1,400	....	....
11/17/22	3,750	13.5	—	—	....	4.5	....	.....	16.2	106	46.5	27.8	123	33.0	124	64.9	1.91	1,245	1,400	49.0	1.57
11/18/22‡	3,700	11.8	—	—	....	4.9	....	.....	15.1	105	47.5	30.7	—	35.7	...	....	....	1,284	.....	....	....

* Added glycerin 36 gm. to 40 per cent. cream. † Resp. expt. 30 gm. glucose. ‡ Patient up. Total calories required unknown.

might have had a favorable effect on the carbohydrate tolerance. That this was probably not the case became apparent later when other patients were observed to show similar increases in carbohydrate utilization on a similar dietary regimen to which phosphorous compounds were not added.

During Period IV, the carbohydrate intake was slowly increased to 160 gm. without any increase in blood sugar level or in glycosuria. It was considered unwise to continue this increase. That this probably represented the maximum diet which could be tolerated was shown by the fact that on February 10 the sugar excretion rose slightly.

The patient, having been trained to weigh and calculate the composition of his diets accurately, was permitted to leave the hospital on Feb. 13, 1922, to return to work. He was advised to keep his diet within the limits of the diets given on February 11 and 12, allowing him between 1,700 and 1,950 calories. He remained well—the urine being practically sugar free—and at work during the spring and summer following his discharge. He adhered to his diet for a period of six months, after which he ate anything he desired. On Oct. 10, 1922, he caught cold and became ill and weak. He sought treatment from a chiropractor, who prescribed a liberal carbohydrate diet in addition to his manipulations. He was obliged to quit work on October 19. His ankles became much swollen. He returned to Johns Hopkins Hospital for further treatment on Nov. 2, 1922.

Second Admission.—Examination showed practically the same findings as on the previous admission, except that the clinical evidences of acidosis were not so marked. The tendon reflexes in both upper and lower extremities could not be elicited. There were 4,664,000 red blood cells, 9,666 white blood cells and 75 per cent. hemoglobin. An incomplete twenty-four hour specimen showed the presence of more than 200 gm. of sugar and large amounts of acetone and diacetic acid. Roentgen-ray examination of the lungs showed no abnormality.

The patient's progress under treatment can best be followed by reference to the diet and metabolism chart, Table 3, which is graphically represented in Chart 3.

On a diet slightly above the theoretical requirement, there was a rapid development of acidosis, as shown by the rapid fall in carbon dioxid combining power of the blood plasma.

The progress of the acidosis was arrested by substitution of glycerol for carbohydrate in the diet on November 7 and 8, 36 gm. of glycerol being added to 40 per cent. cream. The carbon dioxid combining power rose and continued rising on the subsequent days on which the patient received a submaintenance diet containing only 11 gm. of protein.

From November 7 to 15, quantitative estimation of the excretion of acetone bodies was made. These bodies were calculated as beta-oxybutyric acid. The excretion decreased from 38 gm. on November 6 to 5 gm. on November 9, during which time the carbon dioxid capacity of the blood plasma increased from 29.6 to 47.8 volume per cent. Acetone excretion diminished to 0.69 gm. on November 15, and qualitative tests were negative between the fifteenth and seventeenth, at which time the FA/G ratio was between 1.85 and 2.00. There is a striking parallelism between the amounts of beta-oxybutyric acid excreted and the FA/G ratios, which is brought out graphically in Chart 4 (see also Tables 3 and 4).

A submaintenance diet, 1,240 calories, was continued until November 29. The protein of the diet was kept low, between 11 and 22 gm. The protein metabolism decreased rapidly, but the patient remained in negative nitrogen balance. The sugar excretion decreased slowly until qualitative tests were negative on November 25. The patient gained in weight during this period in which he was receiving insufficient food to cover either energy or protein requirement. This increase in weight is probably due to water accumulation. Slight facial edema was sometimes noticeable.

The blood sugar did not reach normal limits until November 30. Between November 29 and December 8, there was a rather rapid increase in both

protein and carbohydrate content of the diet. On December 8, the blood sugar value was found to be above normal, and on the following day glycosuria was noted. The diet at this time was P. 45, F. 148, C. 72 gm., 1,850 calories. It is apparent, therefore, that the maximum diet which this patient could tolerate on recovery on this admission is definitely less than that which was reached on the former admission. This probably illustrates the downward progression of the course of the disease, which so many observers have noted.

Between November 26 and December 14, the patient received 30 gm. of calcium hexose phosphate daily. As compared with control cases in which none was given, the rate of increase in carbohydrate tolerance does not seem to have been accelerated by phosphate administration.

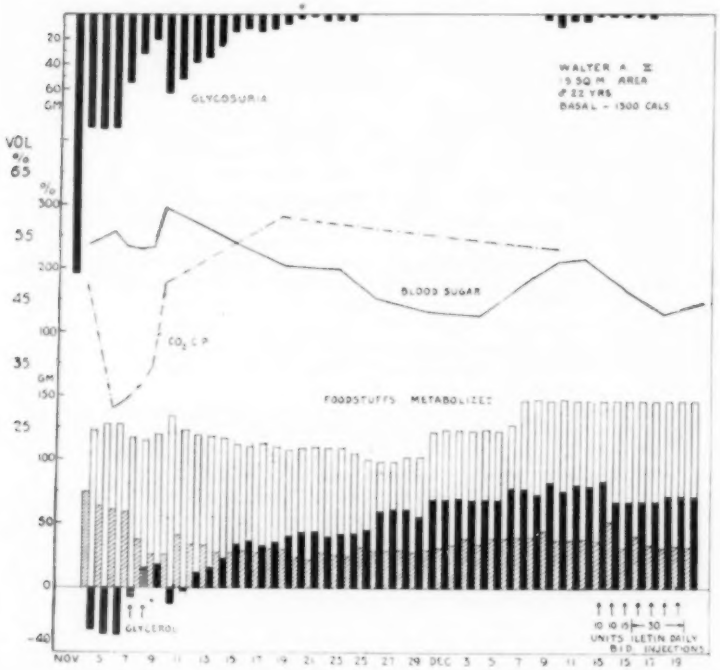

Chart 3 (Case 1).—Metabolism chart of Walter A., second admission. Black columns represent carbohydrate utilized or excreted; shaded columns, protein metabolized; unshaded, fat oxidized. All foodstuffs are given in grams. The diet given is not shown in the graph.

Between December 14 and 21, gradually increasing amounts of "iletin" (insulin, Lilly) were given, until glycosuria was stopped and the blood sugar value was again within normal limits, the diet remaining unchanged (1,850 calories).

Numerous respiration experiments were carried out on this patient. From the basal observations of the respiratory exchange, the basal heat production was calculated and the twenty-four calorie requirement was estimated. These experiments have been reported in a previous communication.[28] The experiments showed a diminished ability to oxidize glucose, as shown by a fall in respiration quotient following the ingestion of glucose.

The basal heat production and respiratory quotients obtained on different occasions are given in Table 5.

CASE 2.—*History.*—Samuel P., was admitted on Jan. 31, 1922, complaining of diabetes. The patient first noticed polyuria, polydypsia and polyphagia in September, 1921. He frequently passed "a gallon of urine a night." His condition became much worse about Christmas, 1921, at which time he was first given dietary treatment by a physician. His symptoms diminished, so that at the time of admission there was no nocturia.

His mother, maternal aunt and maternal grandmother all had diabetes. The family history otherwise was unimportant.

The patient enjoyed excellent health until September, 1921. In 1917, the vision of the right eye was partially destroyed by an electric flash. In the same year, he had a single soft sore on the penis, at the base of the prepuce, which

TABLE 4.—*Ketogenesis in Case 1*

Date	Foodstuffs Metabolized			Total Acetone Bodies Excreted, Gm.	Excess Ketogens Millimols E	Ketogens Total Millimols K	Ketogens Oxidized Millimols K—E=K'	Antiketogens Millimols A	Ratio K : A	Ratio K': A
	Protein, Gm.	Fat, Gm.	Carbohydrate, Gm.							
11/ 6/22	61.5	138	—36.0	57.4	551	618	67	74	8.4	0.9
11/ 7/22	59.4	127	—7.2	36.7	353	578	225	223	2.6	1.0
11/ 8/22	37.8	125	15.8	19.5	188	521	333	281	1.9	1.2
11/ 9/22	26.6	130	17.9	7.8	75	511	436	260	2.0	1.7
11/10/22	26.6	144	—13.4	12.9	124	559	435	94	5.9	4.6
Av. 9 and 10	....	....	....	....	100	535	435	177	3.0	2.5
11/11/22	40.4	143	—2.6	3.1	30	589	559	197	3.0	2.8
11/12/22	33.8	129	11.6	3.0	29	524	495	247	2.1	2.0
11/13/22	33.1	128	15.1	3.5	34	520	486	263	2.0	1.8
11/14/22	28.5	127	23.2	1.1	10	504	494	293	1.7	1.7

TABLE 5.—*Basal Heat Production and Respiratory Quotients*

	Basal Metabolism, Calories per Hour	Respiratory Quotient
Jan. 25, 1922	54.9	0.77
Jan. 29, 1922	62.2	0.75
Feb. 8, 1922	60.8	0.82
Nov. 10, 1922	54.8	0.70
Dec. 22, 1922	65.6	0.76

was treated locally by cauterization. Six weeks later there was a rash which covered his back and chest. One year later, the blood Wassermann reaction was reported positive. He received eight intravenous injections of arsphenamin, and seventy-two injections of mercury into the buttocks. The patient said that he had always been nervous, easily excited, that he drank heavily and smoked excessively. He had always done hard work on a farm. His best weight was 174 pounds (78.9 kg.) in 1919. On admission, he weighed 65 kg. (144 pounds).

Physical Examination.—Temperature, pulse and respiration were normal. The patient's height was 175 cm., and he weighed 65 kg. He was a well developed, somewhat undernourished young white man, lying quietly and comfortably in bed. Respirations were normal in rate and amplitude. There was no odor of acetone on the breath. Over the skin of the face, neck and trunk there were many acne papules and pustules and a great many comedones. Over the back and on the dorsal surface of the right thigh and buttock, there were several furuncles. There were small scars of previous lesions. The lymph

nodes at the angle of the jaw, axillae and inguinal regions were palpable, but not much enlarged or tender. The extra-ocular movements were normal. The left pupil reacted to light directly but not consensually; the right pupil did not react to light directly, but did react consensually. Vision in the right eye was confined to light perception only.

Ophthalmoscopic Examination: The left eye was normal. There was posterior polar cataract in the right eye; this disk outline was blurred, appar-

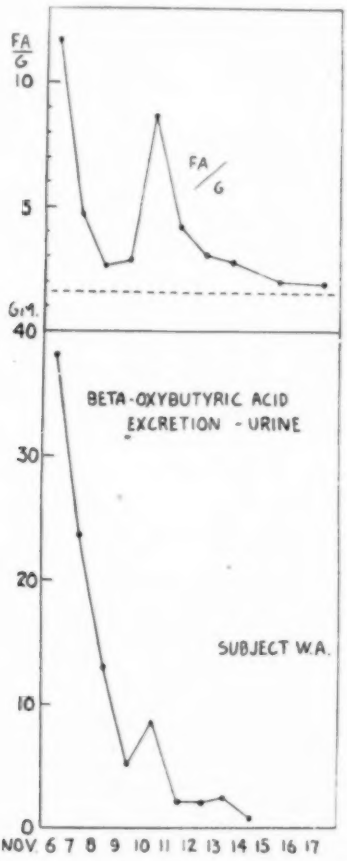

Chart 4 (Case 1).—Ketogenesis. Note Tables 3 and 4.

ently due to lenticular opacity. Extending outward from the disk, there was a streak of connective tissue running upward and to the nasal side until it met an area of choroidal atrophy from which strands of connective tissue extended out into the vitreous. Just below the margin of the disk there was another connective tissue strand also extending out into the vitreous and temporalward to the limit of ophthalmoscopic vision. Diagnosis: Retinitis proliferans. The

lungs and heart were normal. Blood pressure was: systolic, 115, diastolic, 75. There were no other findings of importance except that there was a small white scar on the dorsum of the glans penis.

The urine contained considerable sugar, acetone and diacetic acid. The blood contained 0.22 per cent. sugar.

Diagnosis: Diabetes mellitus, syphilis, acne vulgaris, furunculosis and retinitis proliferans.

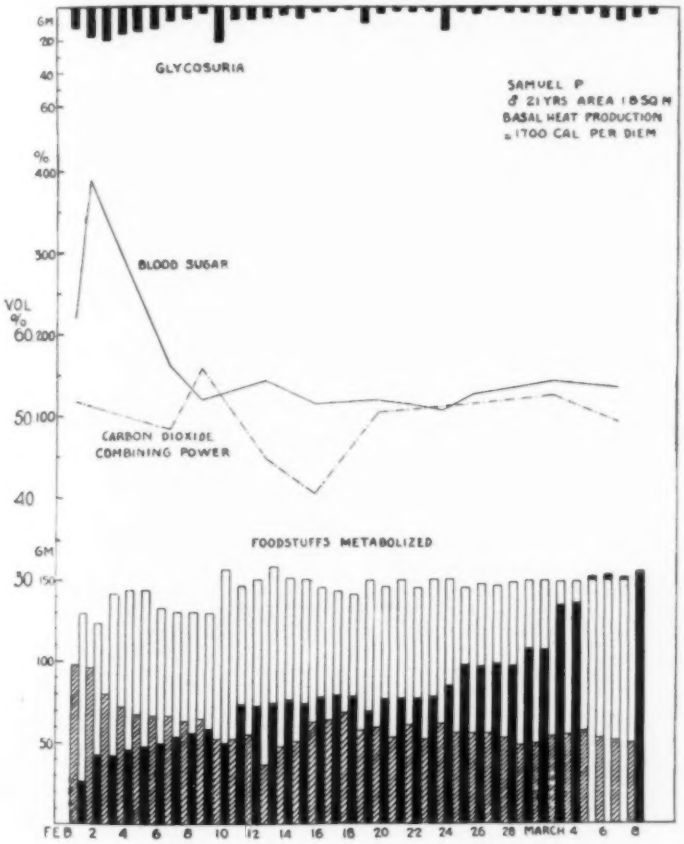
GM
GLYCOSURIA
SAMUEL P
♂ 21 YRS AREA 1.85 SQ M
BASAL HEAT PRODUCTION
-1700 CAL PER DIEM
%
BLOOD SUGAR
VOL %
CARBON DIOXIDE COMBINING POWER
FOODSTUFFS METABOLIZED
FEB 2 4 6 8 10 12 14 16 18 20 22 24 26 28 MARCH 4 6 8

Chart 5 (Case 2).—Metabolism chart. Foodstuffs metabolized are given in grams. The black areas indicate carbohydrate; the shaded, protein; the unshaded, fat.

February 1: Blood Count: Red blood cells, 5,464,000; white blood cells, 8,200; hemoglobin, 99 per cent. Smear and differential count were normal.

February 2: The blood Wassermann reaction was negative.

Comment.—The course of the patient under treatment is best shown in Table 6, which contains all the data relative to diet and metabolism. It is also shown graphically in Chart 5.

TABLE 6.—*Diet and Metabolism in Case 2*

Date, 1922	Urine Analysis								Blood		Diet Received				Foodstuffs Metabolized						Basal Heat Produced	Calories Received	Body Wt., Kg.	Body Surface, Sq. M.
	Volume, C.c.	Sugar, Gm.	Acetone	Diacetic Acid	Total Organic Acid, C.c. N/10	Nitrogen, Gm.	B-oxybutyric Gm.	Ammonia Nitrogen. Gm.	Carbon Dioxid, C P Vol. %	Sugar, Gm.	Protein, Gm.	Fat, Gm.	Carbohydrate, Gm.	Average G. Gm.	Protein, Gm.	Fat, Gm.	Carbohydrate, Gm.	Available G, Gm.	Available F A, Gm.	F A / G				
2/ 1*	.....	13.2	+	+	1,109	15.5	....	....	51.9	0.220	13.0	2.2	38.6	46.4	96.9	144	25.4	96	174	1.8	1,700	226	65.3	1.79
2/ 2	1,700	19.8	+	+	1,176	15.3	....	....	51.2	0.392	44.2	147	62.4	103	95.6	138	42.6	112	167	1.5	.....	1,508	65.9	1.80
2/ 3	2,300	21.7	+	+	1,852	12.7	....	....	....	.....	44.3	147.5	63.5	104	79.4	156	41.8	104	177	1.7	.....	1,814	66.8	1.82
2/ 4	2,450	17.4	+	+	1,784	11.5	....	....	....	.....	44.7	148	62.2	103	71.8	158	44.8	102	175	1.7	.....	1,812	66.7	1.85
2/ 5	2,530	16.3	+	+	1,634	10.7	....	....	....	.....	44.3	148	63.3	104	66.9	158	47.0	102	174	1.7	.....	1,814	67.4	1.84
2/ 6	2,200	14.7	+	+	940	10.6	....	....	48.4	0.161	44.1	3.6	63.4	89	66.2	147	48.7	102	163	1.6	.....	455	66.1	1.80
2/ 7	2,240	9.6	+	0	868	10.6	....	....	....	.....	44.6	1.8	62.6	89	66.2	145	53.0	106	161	1.5	.....	456	66.1	1.80
2/ 8	2,160	6.9	+	0	843	10.1	....	....	....	.....	43.9	2.1	62.2	88	63.1	145	55.3	106	160	1.5	.....	455	66.4	1.81
2/ 9	1,750	4.3	Trace	0	570	10.3	....	....	55.8	0.121	44.3	1.9	62.0	88	64.4	144	57.7	109	160	1.5	.....	454	64.2	1.78
2/10	2,640	22.5	+	0	.....	8.4	....	....	....	.....	45.4	150	71.9	113	52.4	...	49.4	...	...	...	.....	1,873	66.4	1.81
2/11	2,360	8.3	Trace	0	.....	8.4	....	....	....	.....	45.5	150	80.9	123	52.4	...	72.6	...	...	...	.....	1,914	66.3	1.80
2/12	2,600	8.0	Trace	0	.....	8.8	....	....	....	.....	46.6	150	80.3	122	55.0	...	72.3	...	...	...	.....	1,918	66.6	1.82
2/13	1,700	7.4	+	Trace	.....	5.8	....	....	44.8	0.143	45.4	150	80.9	122	36.2	...	73.5	...	...	...	.....	1,916	66.7	1.82
2/14	2,300	5.2	+	Trace	.....	7.6	....	....	....	.....	45.7	150	80.7	122	47.5	...	75.5	...	...	...	.....	1,917	66.6	1.82
2/15†	3,620	7.3	Trace	0	.....	8.2	1.87	....	....	.....	44.8	150	81.0	122	51.2	...	73.7	...	...	...	1,670	1,908	66.1	1.80
2/16	3,600	3.5	Trace	0	.....	10.1	1.23	....	40.6	0.117	46.4	151	80.6	123	63.1	...	77.1	...	...	...	.....	1,922	65.3	1.79
2/17	2,440	2.8	Trace	0	.....	10.3	1.11	....	....	.....	45.8	151	81.3	123	64.4	...	78.5	...	...	...	.....	1,923	64.8	1.75
2/18	2,340	1.9	Trace	0	.....	11.0	1.49	....	....	.....	46.9	151	80.1	122	68.8	...	78.2	...	...	...	.....	1,921	65.2	1.79
2/19	2,880	10.4	+	+	.....	9.3	1.98	....	....	.....	45.8	149	80.9	122	58.1	...	70.5	...	...	...	1,690	1,922	65.4	1.79
2/20‡	2,560	4.0	Trace	0	.....	9.6	1.86	....	50.6	0.120	45.2	151	81.3	123	60.0	...	77.3	...	...	...	.....	1,923	65.5	1.79
2/21	2,480	2.5	Trace	0	.....	8.5	1.53	1.15	....	.....	47.0	151	80.1	123	53.1	...	77.6	...	...	...	.....	1,925	65.0	1.79
2/22	3,640	3.0	V.F.T.	0	.....	9.8	1.31	1.12	....	0.115	46.1	150	80.5	122	61.2	...	77.5	...	...	...	1,545	1,917	64.5	1.81
2/23	2,300	2.5	Trace	0	.....	8.4	1.02	....	....	.....	45.4	152	80.2	122	52.5	...	77.7	...	...	...	.....	1,929	64.5	1.81
2/24	2,900	14.5	Trace	0	.....	9.9	2.29	....	....	0.107	45.4	151	99.7	141	61.8	...	85.2	...	...	...	1,660	2,000	65.3	1.79
2/25	2,770	2.5	Trace	0	.....	9.0	1.32	1.25	....	.....	45.8	150	100.4	142	56.2	...	97.9	...	...	...	.....	1,995	64.9	1.81
2/26	3,600	4.0	Trace	0	.....	9.0	1.05	1.22	....	0.129	46.5	150	101.0	143	56.2	...	97.0	...	...	...	.....	2,000	64.5	1.81
2/27§	2,150	2.0	Trace	0	.....	9.0	0.41	1.12	....	.....	46.4	151	101.1	143	56.2	...	99.1	...	...	...	1,670	2,007	64.8	1.82
2/28	2,300	3.0	Trace	0	.....	8.5	1.06	1.02	....	.....	45.9	151	100.6	143	53.1	...	97.6	...	...	...	.....	2,000	64.1	1.80
3/ 1	3,300	3.4	Trace	0	.....	7.9	....	1.29	....	.....	47.2	150	121.5	164	49.4	...	118.1	...	...	...	.....	2,082	64.3	1.81
3/ 2	2,420	4.3	Trace	0	.....	8.0	....	1.04	52.6	0.123	46.2	150	121.5	163	50.0	...	117.2	...	...	...	.....	2,084	64.1	1.80
3/ 3	3,100	5.0	0	0	.....	8.7	....	1.59	....	.....	46.7	150	140.2	182	54.3	...	135.2	...	...	...	.....	2,158	64.3	1.81
3/ 4	2,500	3.7	0	0	.....	8.8	....	1.12	....	.....	47.9	151	140.1	183	55.0	...	136.4	...	...	...	.....	2,174	64.3	1.81
3/ 5	2,300	8.5	0	0	.....	9.2	....	1.07	....	.....	46.0	152	160.5	212	57.5	...	152.0	...	...	...	.....	2,258	64.3	1.81
2/ 6	3,200	6.4	0	0	.....	8.6	....	1.17	....	.....	46.8	151	159.7	202	53.7	...	153.3	...	...	...	.....	2,248	64.3	1.81
3/ 7	3,150	8.4	0	0	.....	8.3	....	1.09	49.5	1.233	44.9	150	160.2	201	51.8	...	151.8	...	...	...	.....	2,227	64.3	1.81
3/ 8	2,710	6.7	Trace	0	....	6.5	....	0.96	....	.....	47.6	150	160.1	203	40.6	...	154.4	...	...	...	1,600	2,249	64.3	1.81
3/ 9	2,400	4.5	Trace	0	.....	....	....	0.79	....	.....	46.7	150	160.2	...	....	...	155.7	...	...	...	.....	2,241	....	....

* Basal requirement = 1,670 + 170 = 1,840 calories per diem.
† Period I. Tricalcium phosphate, 50 gm. daily.
‡ Period II. Calcium hexo sephosphate, average 30 gm. daily.
§ Period III. Calcium glycerophosphate, 50 gm. daily.

From February 1 to 5, inclusive, the patient was given a diet furnishing only enough calories to cover the basal heat production, of which 10 per cent. of the calories were obtained from protein. Fat and carbohydrate were in the proportions of Woodyatt, F = 2 C plus P/2. On such a diet, very little change in the mount of sugar excreted was observed. The blood sugar fell from 0.39 per cent. to 0.16 per cent.

From February 6 to 9, inclusive, the protein and carbohydrate of the diet were unchanged, but the fat was reduced to the lowest possible figure. At the end of this period, the blood sugar was within normal limits and the sugar excretion much reduced. This was probably only a continuation of the

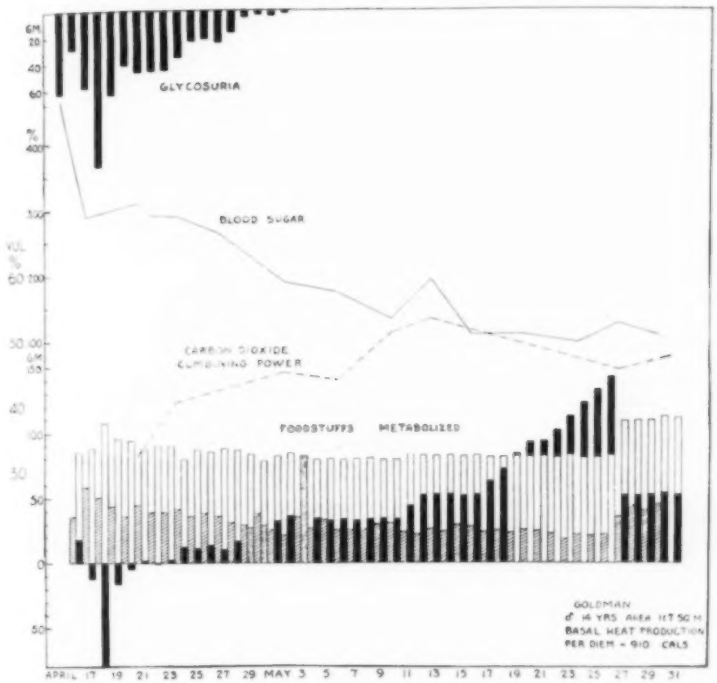
GLYCOSURIA
BLOOD SUGAR
CARBON DIOXIDE COMBINING POWER
FOODSTUFFS METABOLIZED
GOLDMAN
♂ 14 YRS AREA 1.17 SQ M
BASAL HEAT PRODUCTION
PER DIEM = 910 CALS
APRIL 17 19 21 23 25 27 29 MAY 3 5 7 9 11 13 15 17 19 21 23 25 27 29 31

Chart 6 (Case 3).—Metabolism chart. Black columns throughout represent carbohydrate utilized or excreted in the urine. Stippled columns represent glycerol and carbohydrate. Protein metabolism (urine nitrogen grams × 6.25) is shown by the hatched columns. Estimated fat oxidized is shown by the unshaded columns.

improvement initiated in the preceding days. During this last period the excretion of organic acids was much reduced. Diacetic acid ceased to be detected first in the urine of February 7. On this day, the ratio of the available ketogenic substances, FA, to the total available antiketogenic substances, G, was found to be 1.5. The last observed diacetic acid excretion, February 6, occurred when the FA/G was 1.5. A small amount of acetone continued to be excreted throughout the patient's stay in the hospital, but as long as diacetic acid was

TABLE 7.—*Nitrogen, Phosphorus and Calcium Balances in Case 2*

Period	Dates Inclusive	Food N, Gm.	Urine N, Gm.	Feces N, Gm.	Total N Excreted, Gm.	N Balance, Gm.	Food P, Gm.	Added P, Gm.	Total P Intake, Gm.	Urine P, Gm.	Feces P, Gm.	Total P Excreted, Gm.	P Balance, Gm.	Food Ca, Gm.	Added Ca, Gm.	Total Ca Intake, Gm.	Urine Ca, Gm.	Feces Ca, Gm.	Total Ca Excreted, Gm.	Ca Balance, Gm.
I*	Feb. 15-19	36.6	48.9	6.3	55.2	−18.6	5.02	16.70	21.72	5.26	15.32	20.58	+1.14	2.79	38.80	41.59	1.54	25.68	27.22	+14.37
II†	Feb. 20-26	51.4	64.2	12.0	76.2	−24.8	10.09	32.40	42.49	9.17	32.81	41.98	+0.51	4.02	52.61	56.13	1.90	46.40	48.30	+8.33
III‡	Feb. 27-Mar. 6	59.7	68.7	19.3	88.0	−28.3	11.93	52.76	64.69	12.61	55.83	66.44	−1.75	5.03	68.56	73.59	2.17	71.95	74.12	+0.53

* $Ca_3(PO_4)_2$, 100 gm.

† Calcium hexose phosphate, 420 gm.

‡ Calcium glycerophosphate, 400 gm.

not present, the patient was allowed to sit up, so that the fat metabolism could no longer be calculated from the basal heat production.

During Periods I, II and III, as shown in Table 5, this patient was given first inorganic phosphate, $Ca_3(PO_4)_2$, calcium hexose phosphate, and calcium glycerophosphate. During these periods, the actual utilization of carbohydrate increased, although a slight glycosuria persisted. The sugar content of the blood taken before breakfast remained within normal limits. In the light of similar marked improvement observed in cases treated without addition of large amounts of calcium and phosphorus to the diet, the improvement in this case is not attributed to the effect of calcium or phosphorus.

The balance between ingestion and excretion of calcium phosphorus and nitrogen are given in Table 7. In the case of calcium and phosphorus, no comment is offered. Nitrogen balance was negative throughout. This may be due to the large bulk of stools caused by the use of bran agar biscuits.

Respiration experiments on this subject have been reported in a previous communication.[20] The determinations of the basal metabolism and respiratory quotients are given in Table 8.

TABLE 8.—*Basal Metabolism and Respiratory Quotients in Case 2.*

	Basal Metabolism, Calories per Hour	Respiratory Quotients	Percentage of Average Normal
Feb. 15, 1922	69.3	0.75	97
Feb. 19, 1922	70.0	0.83	98
Feb. 22, 1922	64.1	0.77	90
Feb. 24, 1922	68.8	0.80	96
Feb. 27, 1922	70.1	0.77	98
Mar. 8, 1922	67.7	0.83	95

CASE 3.—*History.*—Charles G., a schoolboy, aged 14 years, was admitted to the hospital on April 15, 1922, complaining of loss of weight. The paternal grandmother probably had diabetes. The patient's general health had been excellent. He had had scarlet fever at the age of 8 and measles at the age of 10. In July, 1921, he had had typhoid fever, with which he had been ill for two months. The attack was a mild one without complications. His present illness dated from the convalescence from typhoid fever. He had always eaten heartily. He had frequent attacks of "indigestion" with abdominal pain, vomiting and constipation. These attacks were relieved by rest, restricted diet and castor oil. He was habitually constipated, requiring purgatives most of the time. Before the attack of typhoid fever, the patient weighed 95 pounds (43.09 kg.). Following this, he weighed only 80 pounds (36.28 kg.).

During the typhoid convalescence, an attempt was made to fatten the patient. In October, 1921, he began to drink a large amount of water, about 5 quarts a day. The urinary output increased in proportion. His appetite was unusually good. His weight decreased slowly. Sugar was discovered in the urine, but in spite of this he was given meat and candy and all that he could eat in an effort to make him gain weight. During the month prior to admission he lost 4 pounds (1.81 kg.), the weight on admission to the hospital being 68 pounds (30.84 kg.).

Physical Examination.—The patient's height was 154.5 cm.; he weighed 30.1 kg. The patient was a thin, poorly nourished, rather pale boy of 14 years. The skin was loose from loss of the panniculus. The mucous membranes were somewhat pale. Other than this no abnormalities were found.

The urine showed the presence of large amounts of sugar and acetone bodies. Blood examination revealed: red blood cells, 5,864,000; white blood cells, 5,920;

TABLE 9.—*Diet and Metabolism in Case 3*

Date 1922	Urine Analyses							Blood		Diet Received				Foodstuffs Metabolized						Food, Calories	Calculated Requirement	Body Wt., Kg.	Surface Area, Sq M.
	Volume, C.c.	Sugar, Gm.	Acetone	Diacetic Acid	Total Oxybutyric Acid, Gm.	Ammonia, Gm.	Total Nitrogen, Gm.	Carbon Dioxid, C P Vol. %	Sugar, %	Protein, Gm.	Fat, Gm.	Carbohydrate, Gm.	Average G, Gm.	Protein, Gm.	Fat, Gm.	Carbohydrate, Gm.	Available F A, Gm.	Available G, Gm.	F A / G				
4/15*	1,640	62.3	++++	++++	21.3	2.30	8.47	....	0.465	....	....	....	....	52.9	....	....	....	....	....	....	....	....	....
4/16	1,770	28.3	++++	++++	21.8	2.42	5.69	....	.....	30.8	107	45.9	74.5	35.6	85	17.6	....	....	....	1,310	1,000	30.1	1.17
4/17	2,300	57.5	++++	++++	25.3	3.20	9.24	....	0.290	32.3	107	44.7	74.1	57.7	88	−12.8	....	....	....	1,310	1,000	30 5	....
1/18	2,120	116.6	++++	++++	23.6	3.19	8.10	....	.....	31.0	107	44.7	73.3	50.6	117	−71.9	109.0	....	....	1,306	1,000	30.0	....
4/19	2,500	62.5	++++	++++	18.7	2.65	6.98	....	.....	29.4	107	46.0	73.7	43.6	96	−16.5	109.0	18.4	5.92	1,307	1,000	30.3	....
4/20	2,500	40.0	++++	++++	19.0	2.41	5.68	....	.....	32.1	109	45.4	74 8	35.5	94	−5.4	101.0	24.6	4.10	1,327	1,000	29.7	....
4/21	3,244	45.4	++++	++++	12.5	2.46	7.06	32.4	0,310	29.6	108	46.6	74.4	44.1	88	1.2	99.5	35.6	2.79	1,314	1,000	30.2	....
4/22	3,600	45.0	++++	++++	21.5	2.33	6.23	....	0.291	29.6	108	44.7	72.5	38.9	91	−0.3	99.3	31.3	3.17	1,305	1,000	30.4	....
4/23	3,280	44.3	++++	++++	10.2	1.97	6.22	....	.....	30.7	14	46.2	65.3	38.9	90	1.9	97.5	33.4	2.92	442	1,000	30.8	....
4/24	3,840	34.5	++++	++++	8.3	1.75	6.68	40.6	0.220	31.2	15	46.0	65.4	41.7	80	11 5	90.8	43.7	2.08	455	1,000	31.0	....
4/25	3,250	22.1	++++	++++	9.7	1.54	5.79	....	.....	29.5	81	32.6	62.7	36.1	87	10.5	94.9	50.1	1.88	1,007	1,000	31.3	....
4/26	3,066	20.3	++++	++++	8.7	1.56	6.10	....	.....	31.4	82	33.3	59.6	38.1	85	13.0	94.0	58.6	1.75	1,026	1,000	31.9	....
4/27	3,760	23.5	+++	+++	7.3	1.25	5.75	....	0.265	29.4	82	33.1	58.3	35.9	88	9.6	95.3	39.2	2.43	1,016	1,000	31.4	....
4/28	3,300	16.5	++	++	4.6	1.10	4.95	....	.....	30.6	81	32.5	58.3	30.9	87	16.0	92.3	42.6	2.17	1,012	1,000	32.5	....
4/29†	3,560	4.9	+	—	2.26	0.77	4.63	....	.....	31.1	82	1.2	58.4	28.9	83	27.3	87.8	52.4	1.67	1,026	1,000	32.8	....
4/30†	2,860	3.4	+	—	1.33	0.65	6.01	....	.....	34.1	84	1.2	61.2	37.5	78	28.8	87.7	58.3	1.50	1,058	1,000	32.8	....
5/ 1	3,200	4.0	—	—	0.92	0.57	4.03	....	.....	13.5	2.6	38.2	46.3	25.2	82	32.2	85.4	54.9	1.55	236	1,000	32.7	....
5/ 2	3,540	1.8	—	—	0.79	0.29	3.47	45.3	0.190	13.6	2.6	38.1	46.2	21.7	84	36.3	85.6	57.3	1.49	236	1,000	33.1	1.24
5/ 3‡	3,700	....	—	—	0 05	0.62	5.68	....	.....	31.2	82	1.5	107.8	35.5	82	81.5	91.2	110.9	0.82	1,236	.....	33.5	....
5/ 4	3 940	....	—	—	1.24	0.61	4.26	....	.....	30.7	81	33.9	59.8	26.6	...	33.9	....	....	....	1,022	.....	33.0	....
5/ 5	3,820	....	—	—	1.63	0 65	5.35	....	.....	31.4	82	32.8	59.1	33.4	...	32.8	....	....	....	1,021	.....	32.9	....
5/ 6	4,100	....	—	—	1.51	0.57	4.06	44.0	0.174	31.4	82	33.5	59.8	25.4	...	33.5	....	....	....	1,023	.....	32.6	....
5/ 7	4,200	....	—	—	0.39	0.57	3.99	....	.....	31.4	83	32.5	59 8	24.9	...	32.5	....	....	....	1,031	.....	32.1	....
5/ 8	3,355	....	—	—	....	....	4.03	....	.....	29.0	82	33.7	58 6	25.2	...	33.7	....	....	....	1,019	.....	31.9	....
5/ 9	4,400	....	+	—	3.99	0.65	3.88	....	.....	29.9	84	34.4	60.1	24.2	...	34.4	....	....	....	1,042	.....	31.9	....

* Basal heat production = 910 calories + 10 per cent. (91 calories) = 1,001 calories. † 31 gm. glycerin added to diet. ‡ 80 gm. glycerin added to diet.

hemoglobin, 100 per cent., with a normal differential count. The Wassermann reaction was negative. The blood sugar content was 0.465 per cent.

Comment.—The patient was at first given a diet of 1,300 calories, estimated to cover the normal requirement for his size and age. Subsequently this was found to be greatly in excess of the actual requirement (Table 9). At the end of one week on this diet the sugar excretion had considerably diminished, the blood sugar remaining high. For two days, April 23 and 24, the total calories of the diet were reduced to 450 by diminishing the fat from 108 to 15 gm. The blood sugar remained stationary, the carbon dioxid capacity of the plasma increased, and there was a coincident decrease in excretion of acetone bodies.

The basal heat production was found to be 910 calories a day. On April 25, a diet was given furnishing 1,000 calories for an estimated requirement of basal metabolism plus 10 per cent. The patient was kept in bed and showed little tendency to activity, as he was ill and weak.

Between April 25 and 29, a further decrease in urine sugar excretion occurred and a further diminution in acetone elimination. On the twenty-ninth, the diet formula was unchanged except that 31 gm. of glycerine were substituted for

TABLE 10.—*Ketogenesis in Case 3*

Date	Foodstuffs Metabolized			Total Acetone Bodies Excreted, Gm.	Excess Ketogens Millimols E	Ketogens Total Millimols K	Ketogens Oxidized Millimols K—E=K′	Antiketogens Millimols A	Ratio K : A	Ratio K′: A
	Protein, Gm.	Fat, Gm.	Carbohydrate, Gm.							
4/19/22	43.6	96	—16.5	28.1	270	435	165	92	4.7	1.8
4/20/22	35.5	94	—5.4	28.5	274	407	133	137	3.0	1.0
4/21/22	44.1	88	1.2	18.8	180	408	228	258	1.6	0.9
4/22/22	38.9	91	0.3	32.2	310	406	96	175	2.3	1.8
4/23/22	38.9	90	1.9	15.3	147	402	255	186	2.2	1.4
4/24/22	41.7	80	11.5	12.5	120	376	256	244	1.5	1.1
4/25/22	36.1	87	10.5	14.6	140	385	245	224	1.7	1.1
4/26/22	38.1	85	13.0	13.1	126	384	258	243	1.6	1.1
4/27/22	35.9	88	9.6	11.0	106	389	283	218	1.8	1.3
4/28/22	30.9	87	16.0	6.9	66	373	306	181	2.1	1.7
4/29/22	28.9	93	27.3	3.4	33	354	321	235	1.5	1.4
4/30/22	37.5	78	28.8	2.0	19	358	339	324	1.1	1.04
5/ 1/22	26.2	82	32.2	1.4	13	341	328	306	1.1	1.07
5/ 2/22	21.7	84	36.3	1.2	12	341	329	320	1.1	1.03
5/ 3/22	35.5	82	81.5	0	0	367	367	613	0.6	0.6

31 gm. of carbohydrate. The result was an immediate sharp decrease in both sugar and acetone excretion. Following this, the diet consisted of 1,000 gm. of 5 per cent. vegetables, furnishing only 236 calories. By May 3, glycosuria was no longer present, and only minimal amounts of acetone bodies were excreted.

From the data available in this case, it is possible to calculate the ratio of ketogenic to antiketogenic substances in the patient's metabolism at the time of cessation of ketonuria. Between April 27 and 30, the beta hydroxybutyric acid excretion decreased from 7.3 gm. to 1.3 gm., and the ratios FA/G diminished from 2.43 to 1.50. The ratios at the time of cessation of acetone body excretion lie between the values of 1.49 and 1.55, corresponding closely with the theoretical metabolism of one molecule of diacetic acid with one molecule of hexose (Table 10 and Chart 7).

The further course of the patient was one of rapid improvement. By May 10, the blood sugar was at the normal level, and the alkaline reserve of the plasma was normal. A slight increase in carbohydrate intake resulted in a return of the blood sugar to a higher level on the thirteenth. At this time, administration of calcium hexose phosphate was started. Without decreasing the diet, the

blood sugar again returned to normal levels, and it was possible to increase the diet by increase of carbohydrate from 52 to 142 gm. and of total available glucose from 79 to 159 gm. The increase in diet was discontinued because it was not desirable to push the increase to the tolerance limit. By the use of more fat and less carbohydrate, the patient could take an adequate diet. He was discharged on May 31, with instructions to restrict the diet to from 1,500 to 1,700 calories.

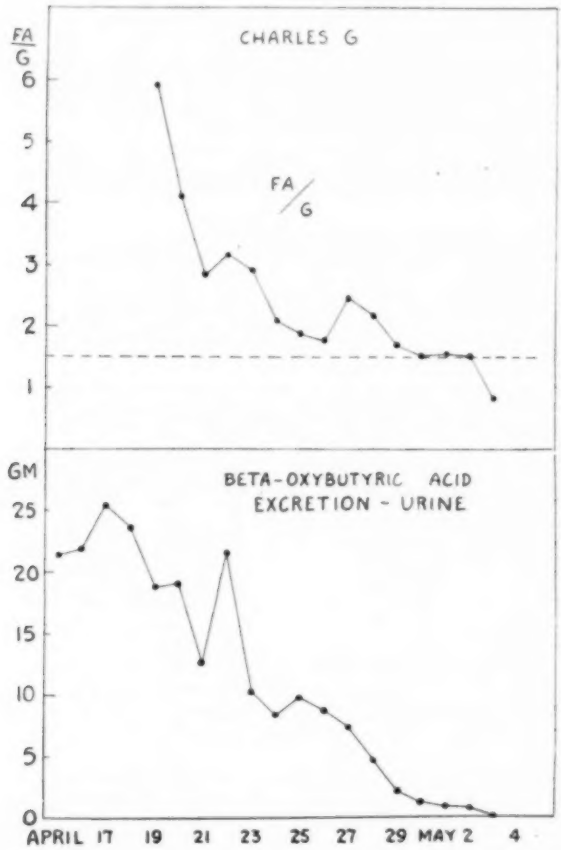

Chart 7 (Case 3).—Ketogenesis. The FA/G ratios were calculated from the amounts of foodstuffs metabolized by the patient, not from the diet given.

Reports from the patient during the summer showed that he was able to keep the urine free from sugar, and several blood examinations showed a normal fasting sugar content.

During the fall and early winter of 1922, occasional glycosuria was reported, easily controlled by the patient himself by means of green vegetable diet.

Reports in December, 1922, and January, 1923, indicate that he was having a great deal of trouble with digestive disturbances and great difficulty on account of constipation.

During the patient's stay in the hospital, he was the subject of several respiration experiments which have been reported in a previous paper.[18] These experiments showed that at the time of marked glycosuria and hyperglycemia there was complete inability to oxidize glucose during a period of two hours after ingestion. There was much greater rapidity of oxidation of ingested calcium hexose phosphate. Coincident with the increase in sugar utilization, respiration experiments showed an improved ability to oxidize glucose ingested.

The basal metabolism tests are summarized below:

April 21: The basal metabolism rate was 25 per cent. below the average normal—37.9 calories an hour × 24 = 910 calories a day.

May 3: The basal metabolism rate was 32 per cent. below the average normal—34.4 calories an hour × 24 = 826 calories a day.

May 8: The basal metabolism rate was 34 per cent. below the average normal—33.4 calories an hour × 24 = 802 calories a day.

May 19: The basal metabolism rate was 36 per cent. below the average normal—32.2 calories an hour × 24 = 773 calories a day.

May 26: The basal metabolism rate was 35 per cent. below the average normal—32.5 calories per hour × 24 = 780 calories a day.

CASE 4.—*History.*—Howard M., a schoolboy, aged 16 years, was admitted July 7, 1922, complaining of thirst and loss of weight. The family history and past history were unimportant. The patient had been in good health until late November, 1920, at which time he noted that he was more thirsty than usual and that he was drinking large amounts of water. Frequent urination was noted, with three or four voidings at night. In spite of a large food intake, a loss of 15 pounds (6.8 kg.) in weight occurred in the course of a few weeks. His weight prior to the onset had remained stationary at about 85 to 90 pounds (38.5 to 40.8 kg.) between the ages of 14 and 16. His first physician prescribed arsenic and water restriction. Two or three weeks later, the urine contained sugar. The diet prescribed was practically carbohydrate free, but allowed unmeasured amounts of fat and protein. Under this regimen, glycosuria continued until March, 1921. At this time, starvation was commenced. The urine ceased to contain sugar. The diet was gradually increased until the patient was comfortable. He gained slightly in weight. In August, 1921, glycosuria was again discovered. From this time on sugar occurred in the urine at intervals of two to three weeks. On each occurrence, the patient was starved until sugar free, and the diet again built up. In this process, only the carbohydrate content of the diet was considered. The amount of carbohydrate which he could take without glycosuria decreased. At the time he left his home to enter the hospital, he had no glycosuria. The diet was much under maintenance, containing only 8 gm. of carbohydrate. In traveling, he again developed glycosuria.

Physical Examination.—The patient's height was 153 cm., he weighed 32 kg. The examination was entirely negative, except for evidence of extreme emaciation, the presence of pyorrhea alveolaris, sluggish tendon reflexes and small characteristic xanthomas situated on the dorsa of the hands between the thumbs and index fingers. The blood pressure was: systolic, 100; diastolic, 75. Temperature, pulse and respirations were normal. Blood examination revealed 4,264,000 red blood cells, 8,200 white blood cells and 70 per cent. of hemoglobin. Blood smear and differential count were normal. The Wassermann reaction was negative. The blood sugar on July 8 was 0.195 per cent. Urine examination showed the presence of sugar but no acetone, albumin or casts.

Treatment and Course.—The course of the patient under treatment can be followed best by reference to the diet and metabolism chart given in Table 11. The patient's dietary requirement was estimated to be about 1,300 calories a

TABLE 11.—*Diet and Metabolism in Case 4*

Date	Urine					Blood		Diet Received				Foodstuffs Metabolized						Calories Received	Body Wt., Kg.	Calories Required
	Volume, C.c.	Sugar, Gm.	Acetone	Diacetic	Total Nitrogen, Gm.	Carbon Dioxid, C P Vol. %	Sugar, %	Protein, Gm.	Fat, Gm.	Carbohydrate, Gm.	Glycerin, Gm.	Protein, Gm.	Fat, Gm.	Carbohydrate, Gm.	Available F A,	Available G,	F A / G			
7/ 8/22*	.....	0	0	0	....	58.8	0.195	31.9	105.4	45.6	..	....	....	....	....	....	....	1,298	32	1,100
7/ 9/22	2,680	0	0	0	?	....	.....	32.2	105.6	45.0	..	....	....	....	....	....	....	1,299	..	.....
7/10/22	3,070	0	0	0	7.77	....	.....	32.0	107.0	45.6	..	48.5	76.8	45.6	91.4	81.5	1.12	1,319	..	.....
7/11/22	3,570	0	0	0	7.63	....	.....	33.3	106.5	44.2	..	47.7	77.8	44.2	91.9	79.7	1.15	1,308	..	.....
7/12/22	3,700	0	0	0	7.95	....	0.175	32.3	105.9	44.9	..	49.7	76.4	44.9	91.7	81.3	1.13	1,301	..	.....
7/13/22	1,840	0	0	0	?	....	.....	33.0	106.6	45.0	..	....	....	45.0	....	....	....	1,311	..	.....
7/14/22	3,340	0	0	0	6.36	....	.....	32.0	105.7	45.1	..	39.7	80.8	45.1	91.0	76.2	1.19	1,299	..	.....
7/15/22	3,460	0	0	0	5.52	....	.....	33.0	106.5	45.7	..	34.5	82.9	45.7	90.5	74.0	1.22	1,313	..	.....
7/16/22	5,050	0	0	0	9.03	....	.....	68.8	106.1	35.6	..	56.4	77.8	35.6	96.9	76.1	1.26	1,415	..	.....
7/17/22	4,740	Trace	0	0	9.78	....	.....	67.8	106.2	35.3	..	61.1	75.8	35.3	96.4	78.3	1.23	1,408	..	.....
7/18/22	4,640	12.9	+	0	9.34	....	.....	68.2	106.5	35.5	..	58.4	82.6	22.6	101.2	64.8	1.59	1,415	..	.....
7/19/22	4,760	36.4	+	0	11.12	....	.....	68.0	105.9	35.0	..	69.5	88.3	—1.4	111.5	48.0	2.32	1,407	..	.....
7/20/22	5,000	30.0	+	0	10.71	....	.....	50.0	109.3	42.3	..	67.0	83.4	12.3	105.9	59.5	1.78	1,395	..	.....
7/21/22	4,460	14.3	+	0	7.99	....	0.267	50.6	109.5	41.8	..	49.9	84.2	27.5	99.7	64.9	1.54	1,406	..	.....
7/22/22	5,210	13.7	Trace	0	8.21	....	.....	51.1	110.5	41.3	..	51.3	83.6	27.6	98.8	65.8	1.50	1,374	..	.....
7/23/22†	3,160	11.0	Trace	0	7.28	....	.....	13.0	4.0	40.0	..	45.6	85.4	29.0	97.9	64.0	1.53	205	..	.....
7/24/22	4,370	18.9	Trace	0	6.97	....	0.232	16.7	118.5	54.5	..	43.6	83.4	35.6	95.2	69.2	1.37	1,356	..	.....
7/25/22	4,280	24.2	0	0	5.65	....	....	12.3	87.0	10.7	30	35.3	95.4	16.5	102.1	46.5	2.20	1,064	..	.....
7/26/22	4,320	24.1	Trace	0	5.22	....	.....	12.5	87.6	10.3	30	32.6	96.8	16.2	102.1	44.8	2.28	1,138	..	.....
7/27/22	4,610	27.3	0	0	4.81	....	.....	12.3	87.0	10.7	30	30.1	99.1	13.4	103.1	40.7	2.53	999	..	.....
7/28/22	4,900	28.0	0	0	5.25	....	0.268	11.8	88.7	10.0	30	32.8	98.5	12.0	103.7	40.9	2.53	1,013	..	.....
7/29/22	4,920	16.2	0	0	?	....	.....	12.5	87.7	10.3	30	....	....	....	....	....	....	1,009	..	.....
7/30/22	7,340	16.1	0	0	5.59	....	.....	12.5	87.7	10.3	30	34.9	87.8	24.2	95.8	53.3	1.80	1,009	..	.....
7/31/22	7,350	13.8	0	0	5.02	....	.....	11.6	88.6	9.7	30	31.4	93.0	25.9	98.2	53.4	1.84	1,013	..	.....
8/ 1/22	6,640	33.3	0	0	6 80	....	.....	25.8	81.6	34.1	..	42.5	99.2	0.8	108.8	35.4	3.07	1,006	..	.....
8/ 2/22	5,700	39.4	Trace	0	6.12	....	.....	25.4	80.6	34.0	..	38.2	103.7	—5.4	110.9	27.2	4.08	992	..	.....
8/ 3/22	6,140	61.4	++	0	6.77	....	0.333	30.2	84.6	34.9	..	42.3	111.3	—26.5	119.6	11.1	10.8	1,052	..	.....

* Basal, 995 calories + 10 per cent. (100 calories) = 1,095 calories required.

† 1,000 gm. green vegetables.

day, though subsequent determination of the basal metabolism (995 calories) showed the basal requirement to be 1,100 calories. Calculation of the fat metabolized is based on the latter figure during the period in which the patient was confined strictly to bed.

The initial diet furnished 1,300 calories daily from July 8 to 16, with 10 per cent. of the total calories from protein. In all diet prescriptions the relation of the foodstuffs is expressed by the formula $F = 2\ C$ plus $P/2$. On this diet, the patient's progress was apparently satisfactory; the urine contained no acetone or glucose; the blood sugar fell at first from 0.195 per cent. to 0.175 per cent. There was a considerable loss of nitrogen daily, so that the amount of protein in the diet was doubled, keeping the same total caloric value of the diet.

The effect of the increase in protein in the diet between July 16 and 20 was most undesirable. On the second day following the increase a trace of sugar appeared in the urine. This was followed by marked glycosuria, which persisted during the whole remaining period of observation.

A green vegetable diet was given on July 23, and for the days following this restriction of the diet to the bare maintenance requirement, with simultaneous reduction of the protein intake to 12 gm., had no appreciable effect on the glycosuria.

For a period of seven days—from July 25 to 31—30 gm. of glycerine were substituted for an equal weight of carbohydrate in the diet. This caused a prompt cessation of acetonuria, which had existed prior to the substitution. It had an interesting effect on the relationship of the calculated FA/G ratio to the disappearance of acetone from the urine, which it is well to discuss at this point.

The first qualitative test for acetone in the urine was obtained on July 18. Prior to this date, the calculated FA/G ratios were all less than 1.5. On the eighteenth, the ratio was slightly more than 1.5 coincident with acetonuria. The ratios increased considerably and then decreased to about 1.5 again, and acetonuria, as measured by qualitative tests, again decreased to a mere trace. A trace of acetone continued to be excreted even when the FA/G ratio fell to 1.37. On the next day, when the substitution of glycerine was commenced, there was a sharp increase in the calculated FA/G ratio (2.2—2.5), with a coincident disappearance of ketonuria. This phenomenon is difficult to explain. It seems probable that the ingested glycerine had produced an antiketogenic effect, even though 40 to 45 per cent. of its weight appeared in the urine as sugar.

After discontinuing the use of glycerine as a substitute for carbohydrate, a further great increase in the FA/G ratio was noted. It is of interest to observe that there was a lag in the appearance of acetone bodies in the urine, none being present on August 1, when the ratio was 3.07. Such a ratio would indicate that two molecular proportions of diacetic acid had been completely oxidized in the presence in the metabolism of one molecular proportion of glucose.

Beyond August 3, the calculation of the amount of fat metabolized had not been carried out for the reason that the patient was no longer confined strictly to bed, making the total heat production impossible to estimate.

The patient continued under observation during seven weeks more. The remainder of the metabolism chart will not be given in detail for the sake of brevity. It may be summarized briefly. The diet was kept at about 1,000 calories, very low in protein. Glycosuria and hyperglycemia persisted throughout, and small amounts of acetone bodies were excreted.

From August 15 to 24, 30 gm. of calcium hexose phosphate were ingested daily without any change for better or worse in sugar utilization.

At various times between August 25 and September 22, the patient was given injections of "Iletin" furnished by the Eli Lilly Company. The preparations of this substance obtainable at that time were of little potency, so that no practical benefit was derived from the treatment.

After leaving the hospital, the patient was again subjected to starvation by his mother. She was able to cause the disappearance of glycosuria by this method, but was unable to build the diet up to more than 700 calories a day.

It is of interest to note that in the respiration experiments which were performed on this patient, the respiratory exchange following the ingestion of glucose showed an approximately normal rate of increase in respiratory

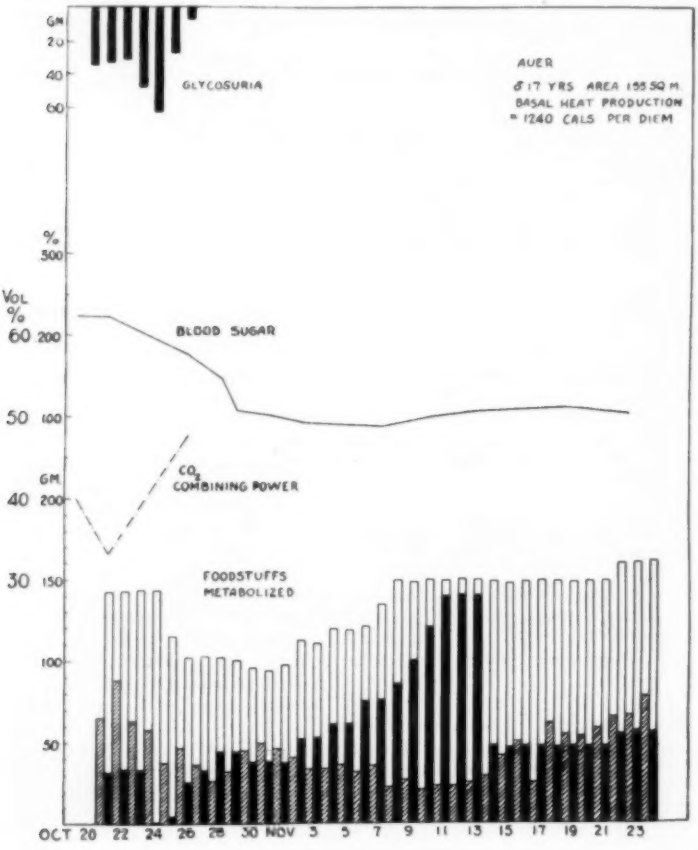

Chart 8 (Case 5).—Metabolism chart. Black columns throughout represent carbohydrate in grams utilized or excreted in the urine. Protein metabolism in grams a day is shown by the cross hatched columns (urine nitrogen grams × 6.25). The fat oxidized daily is shown by the total height of the unshaded columns; in this case only the roughest estimate of fat was possible because of the activity of the patient.

quotients. These experiments were performed on Sept. 5, 1922. They have been reported in the first paper of this series.[23] The basal metabolism on this occasion was 16 per cent. below the average normal, giving a basal heat pro-

duction of 995 calories a day. The basal requirement for the period of confinement to bed was estimated at 10 per cent. above this figure, in round numbers 1,100 calories.

CASE 5.—*History.*—Auer, a schoolboy, aged 17 years, was admitted to the hospital on Oct. 19, 1922, complaining of thirst, excessive urination and of feeling tired. His family history was essentially negative. His past history was negative, except that he had had whooping cough in infancy and two attacks of pneumonia, at the ages of 7 months and 7 years. His health had been excellent in every way. He had led the active outdoor life of a schoolboy, participating in athletics until the onset of the present illness, which began three weeks prior to admission. The onset was sudden, with excessive thirst and polyuria. A week later the patient noted a feeling of weakness and tired easily. His weight, which had been 126 pounds (57.15 kg.) decreased to 114 pounds (51.71 kg.) in three weeks. Sugar was found in the urine by his physician, who sent him at once to the hospital.

Physical Examination.—The patient's height was 171 cm., and he weighed 50 kg. He was a ruddy faced boy, tall, erect, but rather thin. The examination revealed no abnormalities except extreme dryness of the skin and diminished tendon reflexes, the knee jerks being absent. The blood contained 5,800,000 red blood cells and 9,160 white blood cells. There was 95 per cent. of hemoglobin. The Wassermann reaction was negative. The blood sugar was 0.223 per cent., the carbon dioxid combining power 40 volumes per cent. Urine: Specific gravity, 1.055; sugar, heavy reduction; a heavy trace of albumin; acetone and diacetic acid were present. The course of illness under treatment can be outlined best by reference to Table 12, in which are given the data regarding diet and metabolism. A graphic metabolism chart is shown in Chart 8. Reference to Table 12 shows that the FA/G ratio at the threshold of ketonuria indicated approximately the metabolism of two molecules of ketogens per molecule of antiketogen.

For the sake of brevity the portion of the chart beyond November 2 has been omitted, as the progress of the case is shown graphically in Chart 8.

The diet given on discharge from the hospital furnished nearly 2,000 calories. The patient could live on this by restricting activity, but it was far below that required by a normal boy of his age.

ANTIKETOGENESIS

The calculations of the ratios of ketogenic to antiketogenic substances in our series have all been based on the estimates of the amounts of the various foodstuffs oxidized each day. So far as protein metabolism is concerned, the results are quite accurate. It is highly probable that the difference between the amount of carbohydrate ingested and the amount excreted is oxidized, especially when the amount is small. The most questionable calculation is that regarding the amount of fat oxidized, which depends for its reliability on the accuracy with which the total heat production for the day is estimated. In the cases in which the ketogenic balance have been determined, considerable effort was made to keep the energy expenditure as near to the measured basal heat production as possible. The first four cases of this report were kept extremely quiet, and it is highly probable that the estimates of daily heat production (basal metabolism plus 10 per cent.) are within 100 calories of the actual metabolism. This would give an accuracy to the fat estimates of ± 10 gm. a day.

TABLE 12.—*Diet and Metabolism in Case 5*

Date	Urine					Blood		Diet Received			Foodstuffs Metabolized						Calories Received	Calories Required	Body Wt., Kg.	Surface Area, Sq. M.
	Volume, C.c.	Sugar, Gm.	Acetone	Diacetic	Total Nitrogen, Gm.	Carbon Dioxid, C P Vol. %	Sugar, %	Protein, Gm.	Fat, Gm.	Carbohydrate, Gm.	Protein, Gm.	Fat, Gm.	Carbohydrate, Gm.	Available		F A G				
														F A, Gm.	G, Gm.					
Oct. 19-20	.....	....	+	+	....	40.2	0.223	....	.....	....	....	...	....	...	..	...	.....	.....	....	....
Oct. 20-21	1,670	26.9	+	+	15.9	....	.....	....	.....	....	....	...	....	...	..	1.6	1,606	.....	50.5	1.56
Oct. 21-22	900	34.7	+	+	10.8	33.1	0.222	18.7	142.9	65.8	65.5	104	31.1	...	..	1.3	1,658	.....	48.0	....
Oct. 22-23	1,300	32.5	+	+	14.2	.. ..	.....	18.3	142.7	65.6	88.0	93	33.1	123	93	1.5	1,660	.....	....	....
Oct. 23-24	2,300	50.0	+	+	10.0	....	.....	20.4	143.1	65.2	63.0	104	32.7	123	80	2.9	1,656	.....	....	....
Oct. 24-25	2,940	64.9	+	0	9.2	....	.. ..	19.5	143.1	65.8	57.5	120	0.7	134	46	3.4	1,144	1,360	....	....
Oct. 25-26*	2,350	28.2	?	0	6.1	....	.....	19.3	99.5	32.3	37.5	128	4.1	133	39	2.0	1,150	.....	....	....
Oct. 26-27	3,000	8.8	0	0	7.5	47.8	0.175	18.9	99.2	33.8	46.5	115	25.0	125	64	...	1,148	.....	....	....
Oct. 27-28	2,480	0	0	0	5.7	....	.....	19.1	99.9	32.7	36.7	93	32.7	...	..	...	372	.....	....	....
Oct. 28-29	1,820	0	0	0	4.2	....	0.127	15.0	3.1	44.6	25.9	102	44.6	...	..	...	370	.....	....	....
Oct. 29-30	3,140	0	0	0	5.2	....	0.107	15.0	3.1	44.0	32.4	100	44.0	...	..	...	1,124	.....	....	....
Oct. 30-31	2,420	0	0	0	7.2	....	.....	26.0	94.2	37.9	44.9	...	37.9	...	..	...	1,143	.....	....	....
Oct. 30- 1	2,830	0	0	0	7.9	....	0.102	25.5	94.4	37.8	49.4	...	37.8	...	..	...	1,169	.....	....	....
Nov. 1-2	1,950	....	....	...	7.4	....	.....	27.0	97.2	37.8	46.4	...	37.8	...	..	...	1,372	.....	....	....
Nov. 2-3	2,300	....	....	...	6.5	....	0.094	27.9	112.5	51.7	40.3	...	51.7	...	..	...	1,322	.....	....	....
Nov. 3-4	2,250	....	....	...	5.3	....	.....	28.8	110.8	52.5	33.2	...	52.5	...	..	...				

* Basal metabolism = 1,240 calories + 10 per cent. (124 cals.) = requirement, 1,364 calories.

A comparison of the results of computing the ketogenic balance by means of Woodyatt's factors [12] or by those of Shaffer [11] shows that the estimate of ketogenic substances is generally about 15 per cent. higher when Shaffer's factors are used. The difference in the two methods is not sufficient to alter the general interpretation of the results (see the last three columns of Table 10). Woodyatt's ratio $\frac{FA}{G}$ is the ratio of the weights of ketogenic to antiketogenic materials. It is readily converted into a molecular ratio by dividing 1.5, so that it becomes $\frac{FA}{1.5\,G}$, and is approximately the same as K/A = 1/1.

A graphic illustration of the close parallelism between the FA/G ratios and the excretion of B-oxybutyric acid on corresponding days, in two patients, is given in Figures 4 and 7. In Figure 7, the ketonuria ceased sharply at the point at which the FA/G ratio = 1.5, corresponding to a molecular ratio of 1 : 1. In Figure 4, the ratio at which ketonuria ceased is somewhat above this figure, FA/G = 2.0 or a molecular ratio of 1.3 : 1.

At the point of disappearance of ketonuria, the FA/G ratio is almost always close to 1.5 : 1. During the first admission of Walter A., Table 1, acetonuria ceased on January 4, when the FA/G ratio was 1.8, indicating a molecular ratio of 1.2 : 1. During the second admission of this patient (Table 3), ketonuria ceased when the FA/G ratio was 1.9. In the case of Samuel P., ketonuria became negligible when the FA/G ratio was 1.5 (Table 6). Also in the case of Charles G. (Table 9), the same ratio was obtained on the last days of ketonuria.

In the case of Howard M. (Table 11), tests for acetone in the urine were negative prior to July 18. At the threshold of ketonuria in this case, the FA/G ratio changed from 1.2 on the seventeenth to 1.6 on the eighteenth. At the point of disappearance of the ketonuria, a much higher ratio was found, FA/G = 2.5. On the recurrence of ketonuria, the FA/G ratio was slightly over 3.0, indicating the existence of a molecular ratio of K/A = 2 : 1.

The foregoing calculations of the ketogenic balance show that usually, but not always, the molecular ratio is 1 : 1 at the threshold. When excessive ketogenesis exists, Shaffer [11] found that predictions of the ketone excretion based on the equimolecular ratio were too high. In Table 4 and Table 10 a calculation has been made of the ratio of molecules of completely oxidized ketogens to completely oxidized antiketogens. In order to determine this relationship, the total ketone bodies excreted were taken as equal to the amount excreted in the urine plus 50 per cent. to allow for excretion through the lungs.[11] Since the determination of keto acid was expressed in terms of beta-oxybutyric acid, the weight of beta-oxybutyric acid divided by 0.104 gives the number of millimols of ketogenic material excreted. If the total number of ketogenic millimols (K) is known, and from this number one subtracts the number of millimols excreted (E), the difference

(K′) represents the number of millimols of ketogens completely oxidized. In the case of Walter A. (Table 4), K′/A ranged in value from 0.9 to 2.5, and in the case of Charles G. (Table 8), K′/A varied from 0.9 to 1.8. Even at the point of disappearance of ketonuria in the case of Walter A. (Table 4), the ratio of K′/A was 1.7 : 1.

RESULTS OF DIET REGULATION

The plan has been to cover the maintenance requirement of every patient with a diet low in protein, at first, containing the proportion of at least one molecule of antiketogenic substance to each molecule of ketogenic substance in the diet. Four of the five patients described in this report have shown rapid and marked improvement. The failure of one case in five represents an unduly high proportion of failures to the total number of cases treated in this way (about 100 cases). A separate report of the whole series will be made, which will give an idea of the general results achieved.

Regarding Case 4, in which treatment by this method was unsuccessful, it was recognized from his previous history and from his record after leaving this clinic that he could have been rendered sugar free by starvation. It was never possible to keep him sugar free on a maintenance diet. The patient was already in such an emaciated condition and in such constant suffering from hunger that it was not believed to be justifiable to increase his suffering by a futile starvation treatment. Specific insulin therapy need not be further discussed in this case than to state that the insulin at that time was not potent in the amounts available.

There were several temporary departures from the general plan of treatment in these cases. Days on which only green vegetables were eaten were occasionally interpolated and were usually found to hasten the cessation of glycosuria. In diabetic patients who were overweight it was sometimes found to be advantageous to furnish only the protein and carbohydrate in the amounts calculated for a maintenance diet, causing the patient to burn body fat. Reduction in weight in this way is easy and beneficial. Of our present series of five cases, none of the patients was overweight, so that this procedure will be best illustrated in a report of the whole series.

The substitution of an equal amount of glycerol for the calculated amount of carbohydrate in the diet is often of value in reducing glycosuria, and especially in reducing ketonuria. Such a result is well illustrated in Case 3, Charles G. Cremer[26] studied the conversion of glycerol into sugar. In his experiments on phlorrhizinized dogs the sugar excreted in excess of the maximum D : N ratio of 3.65 represented only

26. Cremer, C. G.: Physiologie des Glycogens, Ergebn. d. Physiol. **1**:888, 1902. The work of Külz and von Mering is quoted and an extensive bibliography is given.

about 40 per cent. of the weight of glycerol ingested. It is apparent that so far as the remaining 60 per cent. of glycerol were oxidized, it would be available for antiketogenesis without increasing glycosuria or hyperglycemia. The energy value of a gram of glycerol is 4.3 calories, according to Emery and Benedict.[27]

In a previous communication experiments were reported on the effects of glycerol on the respiratory exchange.[26] It was found that almost identical curves of changes in the respiration quotient were produced by glycerol and glucose when compared in the same diabetic subject. With normal subjects, ingestion of glycerol produced a fall in respiratory quotients. It seems highly probable that glycerol may be oxidized in the body in large amounts. This oxidation may proceed in stages as from glycerol to glyceric aldehyde, so that the oxygen consumption in the early stages would outweigh the carbon dioxid production, resulting in lower quotients than those to be expected from the complete immediate oxidation of glycerol.

One word of warning in regard to the use of glycerol must be given. Some persons appear to be sensitive to glycerol, or to an impurity in it. Vomiting and diarrhea occasionally occurred, and in some subjects urticarial eruptions have been noted. These undesirable effects are noted on the occasion of the first dose, if they are noted at all. When they occur it is not advisable to repeat the dose.

An important point in the therapy of diabetes is the control of the level of protein metabolism. Carefully studied patients with complete diabetes (D:N = 3.65) have almost always shown the disease in its maximum severity following a high protein-fat regimen. In the present series, Case 4, Howard M., illustrates very well the unfavorable effect on the carbohydrate tolerance produced by raising the level of protein metabolism. It is difficult to explain just how this unfavorable effect is brought about. In our larger series of cases, similar observations have been made again and again.

During diabetic acidosis the level of protein metabolism is invariably high. It is rarely to be found to furnish more than 30 per cent. of the total number of calories, even in severe acidosis. In the case of Walter A. (Table 1), Dec. 18, 1921, the calories derived from protein would have been about 45 per cent. of the total heat production were none of the heat of protein lost, the highest percentage of protein metabolism observed in the entire series. As acetonuria diminishes and more calories are obtained from carbohydrate and from the more completely oxidized fat, protein metabolism diminishes. It has been the practice in this clinic to make the proportion of protein calories to total calories quite low in the initial diets (5 to 10 per cent.). When the

27. Emery and Benedict: Am. J. Physiol. **28**:301, 1911. These authors give a heat value of 4,323 calories per gram for pure glycerol.

patient's protein metabolism has reached its minimum, the protein of the food should be increased slowly to attempt to establish nitrogen balance at as low a level as possible (15 per cent. of the total number of calories or less).

By the use of the methods of diet adjustment illustrated in the preceding five cases, it has been found possible to render the vast majority of diabetic patients sugar free without reducing the diet below the maintenance requirement. The disappearance of sugar from the urine is not so rapidly accomplished as by the use of starvation. However, it is believed that if one takes into account the time required in slow building up of the diet after starvation, that time is saved in getting patients to utilize adequate diets. Not only is time saved, but much suffering on the part of the patient is avoided.

Some patients cannot be rendered free from glycosuria by these methods. With such patients, diet restriction is futile in the absence of other means of increasing carbohydrate utilization. Fortunately, the means of accomplishing this are at hand in insulin. Case I received treatment with insulin for a short time.

Discussion of the therapeutic use of insulin will be reserved for a later publication. In the series of insulin treated cases the diets were adjusted in the manner described here, so that the patients of this series will serve to a certain extent as controls to those of the insulin series.

SUMMARY AND CONCLUSIONS

1. Calculations of the ketogenic-antiketogenic balance from the foodstuffs actually metabolized in diabetic subjects show that a maximum of one molecule of antiketogenic substance is required for the complete oxidation of one molecule of ketogenic substance. Frequently less than one molecule of antiketogens will suffice.

2. The records of five patients serve to illustrate both successes and failures of a method of diet adjustment, the aim of which was to afford each patient: (*a*) at least enough calories to cover the maintenance requirement for rest in bed (basal metabolism plus 10 per cent.); (*b*) to reduce the level of protein metabolism by means of a low protein intake; (*c*) to give the foodstuffs in such proportions that at least one molecule of antiketogenic substance will be available for every molecule of ketogen formed.

3. The substitution of glycerol for carbohydrate is a successful means of combating ketosis in certain cases.

4. The improvement noted in patients to whose diet calcium and phosphorus were added (as $Ca_3[PO_4]_2$, calcium hexose phosphate, and calcium glycerophosphate) is not attributed to the effect of this addition.

SOME INTERESTING CASES OF CALCAREOUS DEGENERATION FOUND IN THE THORAX

J. S. PRITCHARD, M.D.

BATTLE CREEK, MICH.

Before considering the following cases of calcareous degeneration found in the thoracic region, a brief review of the subject seems advisable. The chemical, physical and clinical evidences of pathologic calcifications have been noted from time to time for many years; interesting cases have been reported in the literature and important treatises written regarding cause and effect.

Aristotle and Galien [1] mentioned cases of "stone in the lung" in their records. Sommering [2] in 1769 wrote of a case of pulmonary calcification which he considered as a secondary manifestation (metastasis). In 1824, Rullier [3] reported a case of primary calcification of a right upper lung in which a great number of calcified fragments were found. Furhmann [4] thought that the deposition of calcium salts might follow any chronic irritation of the body tissues, and that this explanation accounted for "exercise bone" (calcium formation in deltoid muscle) and "the riders' bones," which proved to be calcium deposits in the adductor muscles of the thigh of persons subjected to prolonged irritation due to horseback riding. Years ago Morton [5] found a special type of consumption which he termed "stony phthisis" on account of the frequent occurrence of stonelike deposits in the expectoration of a patient suffering from the pulmonary form of the disease. In 1858, Virchow wrote extensively on this subject and described necropsy evidence of calcium deposits in the lungs, stomach, kidneys, intestines and blood vessels.

Two types of calcification have been described; the morbid, which follows definite pathologic changes; and the type which might be termed physiologic and which we often find among the manifestations of senility.

The cause of calcareous degeneration has been the subject of much splendid experimental investigation, and in summarizing the probable factors one is impressed by the fact that no specific cause can account for this form of degeneration; that a number of condi-

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1. Aristotle and Galien, quoted by Frozzi, F.: Sopra un caso di calcalosi pulmonare, Gazz. med. de Roma **38**:562, 1912.
2. Sommering, quoted by Osslan, R.: Contributo all studio dell' ossipcazione del pulmone, Riv. osp., 1913, p. 111-337.
3. Rullier, quoted by Osslan, R.: Footnote 2.
4. Furhmann: Ueber einer Fall von pleuritis calculosa, München, 1908.
5. Morton, quoted by Frozzi, F.: Footnote 1.

tions are accountable for abnormal calcareous deposits in the various body tissues is apparent. The most striking conclusion concerning the etiology of this phenomenon is that any chronic irritation, either chemical, mechanical or infectious, may cause a pathologic calcareous degeneration of the tissues involved. Necrosis and suppuration are a common predisposing factor in deposits of calcium salts, especially in the pleura.

Virchow thought that the phenomenon of calcification was due to a superabundance of calcium salts in the blood and that inadequate kidney elimination might also be a causative factor, as many of his cases were associated with advanced renal disease. Virchow believed, too, that the deposits occurred more frequently in organs rich in blood supply; he also made the interesting, and since proved accurate, observation that many cases of pulmonary calcification were associated with destructive bone lesions.

Chiari,[6] a few years after Virchow made his observations, found extensive lime deposits in the lungs without any changes in the osseous structures. Kischenski[7] came to similar conclusions later. In the late seventies Litten[8] advanced the theory that, in the formation of calcareous deposits in the kidneys, one or more irritants acted on certain tissues, like the tubules, and caused an induration of the epithelium followed by a degeneration of the protoplasm. This affected area had an affinity for lime salts carried to it by the blood and lymph.

By experiments on animals, Leik[9] showed that the amount and velocity of the blood supply to the tissues had some bearing on the subject of calcification; he also demonstrated that it was possible to obtain bone formation in the pelvis of the kidney in a rabbit by ligating the renal artery, the calcification occurring in the kidney from sixteen to twenty days later. He wrapped the kidney with omentum and thus established a collateral circulation; if this were not done, three months' time was required to produce calcification. In other words, change in the amount, force or rate of flow of blood supplied to the part was a causative factor in calcareous degeneration. Von Recklinghausen[10] also showed that calcification occurred in tissues poor in blood supply and that this process could proceed when the calcium content of the blood was normal.

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6. Chiari: Wien. med. Wchnschr. **1**, 1878.

7. Kischenski: Ueber Kalkablagerung in den Lungen und im Magen, Med. Oborcye, Dez., 1900.

8. Litten: Ztschr. f. klin. Med., 1879.

9. Leik: Heteroplastische Knochenbildung in Nieren, Arch. f. klin. Chir. **85**: 118, 1908.

10. Von Recklinghausen, quoted by Klotz: Exper., 1905, p. 633.

Important studies regarding etiology were made by Heller and Stade [11] who, however, reached no final verdict from the consideration of many cases from the standpoint of occupation, age and sex; chemical studies as well, failed to reveal anything definite which could be regarded as a probable cause. Aschoff [12] believed that some organic substances like hyalin or fibrin had an affinity for calcium and that the presence of these was necessary for the early formation of calcification.

Gideon Wells [13] published several articles on this phenomenon, and his splendid Harvey lecture is a most complete essay on research in this field. Among many important conclusions he showed that the deposits of lime salts were similar in physiologic and pathologic processes, and that frank calcification might occur in the absence of a definable pathologic etiology. He concluded that the process was possibly a calcification of protein substances which have an elective choice for lime salts and that such a phenomenon was not a chemical reaction. He also showed clearly that such changes were found in rickets, osteomalacia and osteoporosis; thus the chemical and the physical behavior of calcification are important in the solution of questions pertaining to regeneration and repair of bone. Wells emphasized the distinction between calcification and ossification, and later showed that a soft, foreign substance, like gelatin, would cause the precipitation of lime salts.

Von Kossa [14] believed that a diet rich in calcium should be considered as a cause of calcification and proved by animal experiments that food rich in lime caused calcium deposits in the kidneys of the treated animal.

Hueck [15] who has studied this subject extensively, stated that his observations led him to conclude that calcification is not connected with any particular process or disease.

Metastatic calcification occurs in many instances. Askanazy [16] reported that twenty-nine cases in the literature show calcium deposits in healthy tissue of the lungs, kidneys or gastro-intestinal tract. Of

11. Heller and Stade, quoted by Hueck: Centralbl. f. allg. Path. u. path. Anat. **24**:4.

12. Aschoff, quoted by Hueck: Footnote 11.

13. Wells, H. G.: Calcification and Ossification, Arch. Int. Med. **7**:72 (June) 1911.

14. Von Kossa: Ueber die im Organismus kunstlicherzeugten Verkalkung, Beitr. z. path. Anat. u. z. allg. Path. **20**:163, 1901.

15. Hueck: Ueber Verkalkung von Alveolarepithelien, Centralbl. f. allg. Path. u. path. Anat. **24**:4, 1913.

16. Askanazy: Beitrage zu Knocherpathologie Festschr. f. Jaffe, Burnswick, 1901.

this number, all but four cases showed definite destructive bone disease.

Hofmeister and Tanaka [17] caused extensive calcium metastases in the lungs, stomachs and kidneys of rabbits by intraperitoneal injections of soluble calcium salts. These authors called attention to the fact that the organs in which the metastases occurred were also the chief organs which excrete acid. Kalase [18] made similar experiments and came to the same conclusions concerning the metastases in the kidneys, lungs and stomach caused by intraperitoneal injections of soluble calcium salts.

The idea that some endocrine disturbance might be of etiologic significance was propounded by Harbitz [19]. He mentions two kinds of pulmonary calcification; the type following bone lesions (metastasis) and a primary variety not associated with any osseous degeneration.

An interesting case of pulmonary calcium metastasis is reported by A. W. Crane.[20] Here the lung calcification was the remote result of a primary carcinoma of the prostate with malignant metastasis in the pelvic bones. The disintegration of the pelvic osseous tissue liberated lime salts, which in turn formed a calcium metastasis throughout both lungs.

Deficient nutrition of the tissues was also shown by Borst [21] to result in the deposit of calcium, and this was increased when the tissues were deficient in eliminative powers.

Von Werra [22] made an important contribution to the subject when he showed that experimentally produced calcium in the kidneys of rabbits was sometimes reabsorbed in a few weeks. Maximow [23] proved that such deposits may last a year and then disappear even after secondary ossification has taken place. This brings up the question as to whether or not in our clinical observations we are justified in always considering localized concretions as obsolete. Dunham [24] found that calcified nodules in the lung roots may possess definite caseous centers and that for this reason such pathologic changes should not always be considered as evidence of an obsolete tuberculosis.

17. Hofmeister and Tanaka, quoted by Wells: Footnote 13.

18. Kalase: Beitr. path. Anat. u. z. allg. Path. **7**:516, 1914.

19. Harbitz, Francis: Extensive Calcification of the Lungs as a Distinct Disease. Arch. Int. Med. **21**:139 (Jan.) 1918.

20. Crane, A. W.: Pulmonary Metastasis, Am. J. Roentgenol. **5**:479, 1918.

21. Borst: Die Lehre von den Geschwulsten, vol. 1.

22. Von Werra: Ueber die Folgen des vorübergehende und dauernden Verschlusses der Nierenarterie, Virchows Arch. f. path. Anat. **88**:197, 1882.

23. Maximow: Ueber experimentelle Erzeugung von Knochemarkgewebe, Anat. Anz. **28**:609, 1906.

24. Dunham: Wisconsin State M. J., July, 1921.

By injecting mercuric chlorid into the kidney substance of a rabbit, Tartarini-Galleani [25] produced a lesion which showed signs of calcification after undergoing fibrosis and necrosis.

Distomum pulmonale has been described as a cause of pulmonary calcification by Koehler.[26]

Hess [27] points out that hygienic surroundings plus the addition of sunlight and fresh air, as well as diet, are important influences in the prevention and cure of rickets. The production of rickets in mice through a deficient supply of actinic rays suggests the presence of the definite influence of sunshine on the process of calcification.

In summarizing the evidence as to the cause of calcareous degeneration, the following points may reasonably be considered as having some etiologic bearing:

1. Any irritant to the tissues, either mechanical, chemical or infectious, the latter being a most important factor in the cases presented in this article.
2. Any condition which lowers the vitality of the organism.
3. Changes in the composition, velocity or volume of the blood.
4. Interference with the general or local nutrition.
5. The questionable effect of blood and tissue chemistry.
6. Poor assimilation or deficient metabolism of the involved tissues.
7. Constitutional conditions affecting the general metabolism.
8. Any disease of the osseous system which may cause the liberation of lime salts.
9. Alterations in the tissues which cause retention of chronic irritants, such as necrosis, suppurations, chronic inflammatory changes or traumatism.
10. Special selective power of certain tissues for lime salts.
11. The effect of sunlight on the body tissues and metabolism. The production of rickets in mice through deficient supply of actinic rays suggests the presence of a definite influence of sunlight on the process of calcification.
12. Vasomotor disturbances.
13. Possible influences of endocrine derangements.
14. Variations in the carbon dioxid blood content.
15. Hemorrhage into the tissues.

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25. Tartarini-Galleani: Sperimentale **58**:371, 1904.
26. Koehler, Alban: Grenzen des normalen und Anfaenge des pathologischen in Roentgenbilde, Ed. 3, p. 131.
27. Hess, A. F.: Newer Aspects of the Rickets Problem, J. A. M. A. **78**: 1177 (April 22) 1922.

16. Factors influencing osmosis.

17. After all theories have been propounded, there still remain a goodly number of cases of calcareous degeneration unexplained from the etiologic standpoint.

Few, if any, types of body tissues are immune to calcareous degeneration. After a careful study of the literature, the writer concluded that the peritoneum was perhaps one of the tissues least affected.

Chiari found calcareous deposits in the ampulla of the spermatic cord and in the parietal lobe of the brain. Paton reported a case of extensive calcification lining the walls of a necrosed mass between the pleura and the pericardium in a man 70 years of age. Heuer [28] described an unusual case of a large triangular mass in the right pleural cavity of a patient aged 53. The base of this mass rested on the diaphragm, and the walls contained extensive shell-like calcareous plates; the contents were air and fluid. Pathologic examination gave no specific information except that it was a calcified mass.

L. E. Brown [29] records two interesting cases of lung stones and considered that it was a question whether or not pneumoliths, broncholiths or lung stones were a clinical entity. He emphasized the importance of the bronchoscope and roentgen ray in diagnosis. Frozzi [1] cites a case of lung stone in an Italian girl aged 18. He could not agree with Gallippe or Rosenberg in their theory on etiology (salivary lithiasis). Helbig [30] concluded that lung stone was a comparatively rare disease, and up to the time of his publication found few cases reported in the literature.

Canio [31] described a case of pulmonary calcification which came to necropsy as the result of a chronic dysentery. This is of interest on account of a similar case reported in this article, in which an extensive pulmonary calcification was associated with diarrhea. Kochel [32] made a study of the pulmonary tissue involved in this phenomenon and concluded that the alveolar epithelium was free from deposits.

The more frequent locations in which lime deposits make their appearance are undoubtedly the lungs, pleura, gastric and intestinal regions, the blood vessels, glands, joints, tendons, cartilages and bursae. The peritoneum is perhaps less frequently affected.

28. Heuer: Bull. Johns Hopkins Hosp., April, 1917, p. 153.

29. Brown, L. E.: Pneumoliths and reports of Cases, Cleveland M. J. **16**:21, 1917.

30. Helbig, M.: München. med. Wchnschr., October, 1916.

31. Canio, J.: Analyze chemique de deux calcules pulmonaire trouve a l'autopsie d'un malade mort de dysenterie chronic, Rev. med. d'Afrique du Nord **7**:61, 1904.

32. Kochel: Ueber Kalkinkrustation des Lungengewebes, Deutsch. Arch. f. klin. Med. **64**, 1899.

The ribs and costal cartilages have long been the subject of considerable comment. Calcification of any or all of these has been often mentioned as a suggestive sign of early pulmonary tuberculosis and has also been considered as evidence of a predisposition to the disease. Martins and Lorey [33] believe that the phthisical chest form characterized by the long, flat and slender thorax and the steeply descending ribs, together with an ossification of the first rib, is by no means rare in the tuberculous. Freund, about fifty years prior to this, called attention to the narrowing of the thoracic inlet and its probable association with tuberculosis.

At the Battle Creek Sanitarium Clinic, the author has attempted to make a study of calcification of the thoracic cage. In a series of over 7,000 cases the following has been the routine procedure: At the time of the physical examination of the chest a careful history was taken; the laboratory findings included a Wassermann test; in each case stereoscopic chest plates were secured, which were interpreted by the writer in conjunction with the clinical study; the final opinion was based on a summary of the whole investigation. In this way an opportunity was presented for the study of a large number of roentgen-ray stereoscopic photographs of the chest; nevertheless, it is with considerable hesitancy that any opinion is offered concerning the significance of calcium deposits in the ribs, cartilages or sternum.

From the foregoing study, however, a few points present themselves which may be of some importance: First, the number of cases with frank lesions in the upper portion of the lungs, active or inactive, which show no definite sign of calcification in the thoracic cage is remarkable. Second, extensive calcification of the ribs or cartilages occurs frequently without any pulmonary disease. Third, the long, thin, flat, narrow thorax may be more prone to calcification of the upper anterior part, but in my series I have found a considerable number of calcified deposits in all forms and types of the adult thorax.

In gastric calcification, Hofmeister [34] showed that the interglandular tissue in the upper part of the fundus was the usual location, and he emphasized the fact that the acid secreting glands were also situated in this region.

The pleura is not an uncommon seat of frank calcareous deposits, and it is not difficult to find many references on this in the literature. Empyema, extensive and localized, is perhaps the most important cause; as a rule, these deposits take the form of plaques or platelets. The lower half of the pleural cavity is the more common location when the

33. Martins, F., and Lorey, Alex., in Brauer, Schroder, Blumenfeldt: Handbuch der Tuberculose **1,** p. 726.

34. Hofmeister: Ergebn. d. Physiol. **9**:429, 1910.

pathologic process is extensive; small plaques are found in the middle third of the horizontal plane, while apical patches are not so common except when associated with pulmonary calcification. The clinical history of the case suggests that most of the pleural calcifications are probably not due to the action of the tubercle bacilli. In most cases found in my work, no history of present or past tuberculosis could be elicited, but a definite period of illness associated with what the patient called pleurisy, lung fever or pneumonia was usually admitted—suggesting a nontuberculous infection. Since 1800, the literature mentions many authors who described pleural calcification. Those cases described before the advent of the roentgen ray were, in most instances, mentioned in necropsy reports, death being due to other causes. The roentgen ray has led to an increase in the number of such cases reported.

Among the many authors who have written on the subject of calcium deposits in the pleura, I shall call attention to a few of the more recent, such as Courmont and Tixier,[35] Gabszewicz,[36] Todaro,[37] Sweet,[38] Goulliond,[39] West,[40] Huguem,[41] D'Agata.[42]

The composition of calcareous deposits, especially those found in the glands and arteries, was described by Moore and Williams [43] and the various forms of calcification and ossification were discussed by Moschowitz [44] in 1913. Posharissky [45] found that in twenty-eight cases of lung concretions there was evidence of ossification in seventeen, or 60 per cent., while Darbois [46] thought that the tubercle bacillus was the cause of most pulmonary concretions. Kochel found it difficult to establish the lime content of some protein combinations, such as the products of healthy coagulation and hyaline tissue.

Klotz [47] states that, while much has been written on this type of degeneration, little has been ventured in the explanation of the

35. Courmont, J., and Tixier: Lyon méd. **103**:46, 1904.
36. Gabszewicz: Calcification of Pleura, Gaz. lek. **26**:121, 1906.
37. Todaro, N.: Calcificazioni plurale come esoto do pleurite, Cronica suppurativa comire San Milano, **19**:369, 1908.
38. Sweet, W. S.: Calcification of the Pleura and Empyema, Brit. M. J. **1**: 17, 1911.
39. Goulliond: Resection d'une large plaque calcaire d'origine pleurale, Lyon méd. **107**:350, 1906.
40. West, Samuel: Tr. Clin. Soc. London, **39**:42, 1906.
41. Huguem: Etude anatomique des inflammations chronique des sersuses et de leur effet sur les organes qu'elles recouvrebt, Geneve, 1903, p. 47.
42. D'Agata, G.: Empyema chronica con calcificazione pleurale, Clin. Milano, **23**:24, 1915.
43. Moore and Williams: Liverpool M. Clin. **27**:157, 1912.
44. Moschowitz: Proc. New York Path. Soc. **13**:19, 1913.
45. Posharissky: Beitr. z. path. Anat. u. z. allg. Path. **38**:135, 1905.
46. Darbois, P.: Les calcifications pleura-pulmonaires, Bull. et mém. Soc. radiol. méd. de France **6**:60, 1914.
47. Klotz, Oskar: J. Exper. Med. 1905, p. 633.

process underlying calcification. In a splendid experimental study, he showed that this process was, in all instances, preceded by the deposit of a soapy material which existed in the chronically inflamed tissues. This substance seemed to act as an attraction for the ultimate deposit of lime salts, and as the latter increased the former disappeared.

Wells quotes the interesting theory advanced by Murray and Irving [48] concerning the lime formations in coral reefs, the hypothesis being that the calcium is formed by the action of the sea water, which contains soluble calcium sulphate and ammonia carbonate. The latter

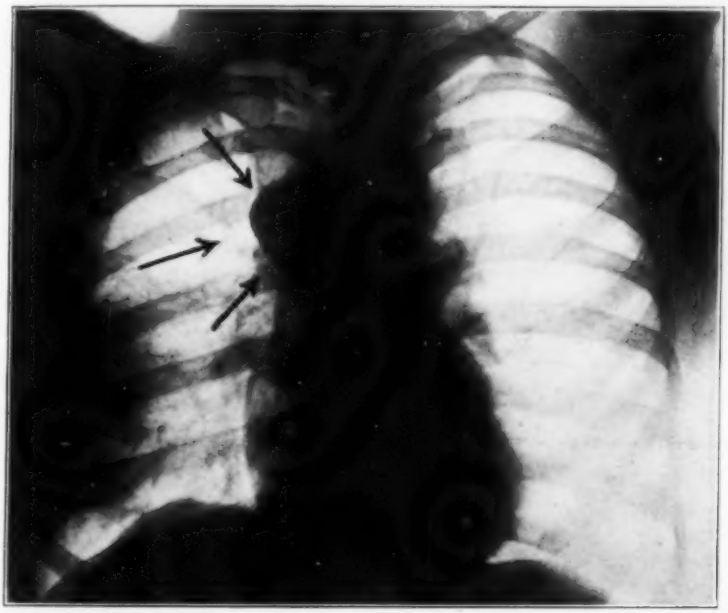

Fig. 1 (Case 1).—Numerous "lung stones" varying in size from that of grains of sand to that of large peas, have been expectorated on five different occasions. After this occurrence, the mass disappears until a redeposit of lime salts occurs in the glandular tissue.

was formed by the metabolism of animal life causing a precipitation of the calcium carbonate. Brown's [29] chemical analysis of the pneumoliths found in his cases shows about the average proportion of phosphate and carbonate as compared with many other estimates. Chemically these concretions were found to contain the following proportions of the ingredients: calcium phosphate, 1.56; calcium carbonate, 0.39; magnesium carbonate, 0.05; and soluble fats, 0.06.

48. Proc. of Roy. Soc. Edinburgh **17**:79, 1889.

The diagnosis of pathologic deposit of calcium was seldom made before necropsy, prior to the advent of the roentgen rays. Occasionally, the grating of a knife or needle coming into contact with a calcified area is the first intimation of the possible existence of such a condition. The history of some past chronic inflammatory process, especially when accompanied by tissue destruction and necrosis, sug-

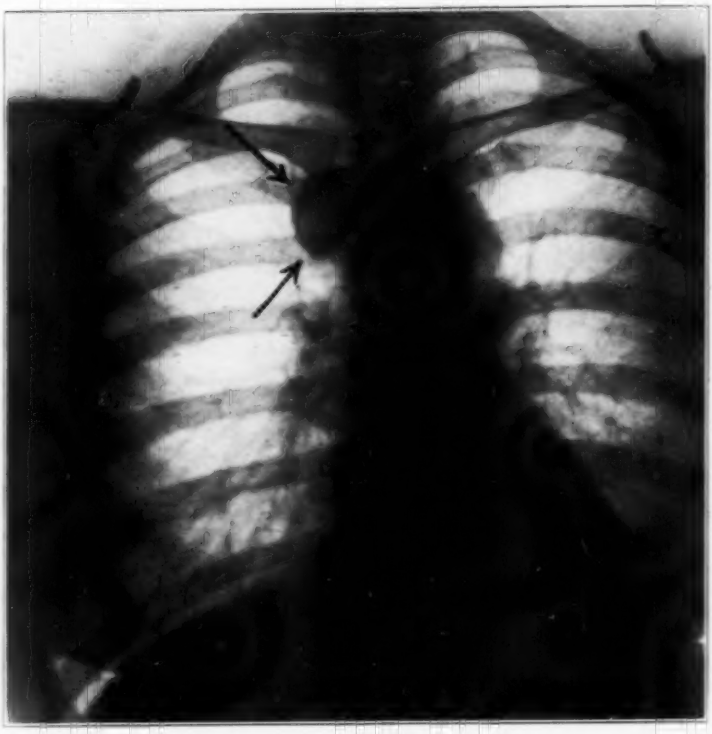

Fig. 2 (Case 2).—Calcified bronchial gland. In this case there was no history of "lung stones."

gests the possibility of some deposits of calcium. This is most reasonably assumed in pleural and pulmonary affections.

Roentgenology has proved the most important help in the diagnosis of this process. The dense, hard, concrete, clean-cut shadow caused by this particular formation is characteristic. Infroit [49] emphasized

49. Infroit: Concretions calcaries du pumon simulant à la radiographiedes eclats d'obus, Bull. et mém. Soc. anat. de Paris **89**:337, 1919.

the value of this method in locating concretions in the lungs, as the roentgen-ray examination was the only method which revealed such a pathologic condition in the three cases cited by him.

Few symptoms occur in the pathologic formation of lime salts. Osslan [2] points out that calcification and ossification frequently occur in the pulmonary substance without causing any clinical manifestations. Brown [29] called attention to the fact that the foreign body action of

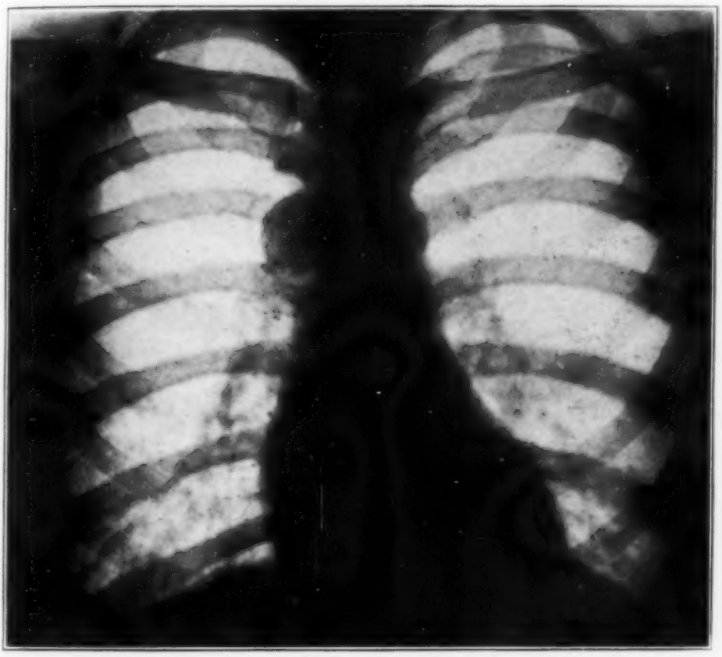

Fig. 3 (Case 3).—The same solid glandular formation in the upper right lung root as seen in Figure 2. There was no history of any past respiratory disturbance which could account for this condition.

pneumoliths must be considered when the symptomology is considered. The concretions form erosions of the bronchi and lung tissue, and the organized infections or abscesses which follow cause the characteristic symptoms of a foreign body. The clinical symptoms, then, depend on the mechanical behavior of the concretions, the possibility of associated infection, their size and location, whether loose or impacted.

In similar lung or pleural affections, the physical findings vary according to the amount and type of the original pathologic process.

The breath sounds and percussion note may be altered, as we find in any fibrosis. This may or may not be associated with a sign of a chronic bronchitis. The physical findings seldom give us much information in the diagnosis of calcium concretions in the chest. The deposit of lime salts is not necessarily a part of a healing or healed process.

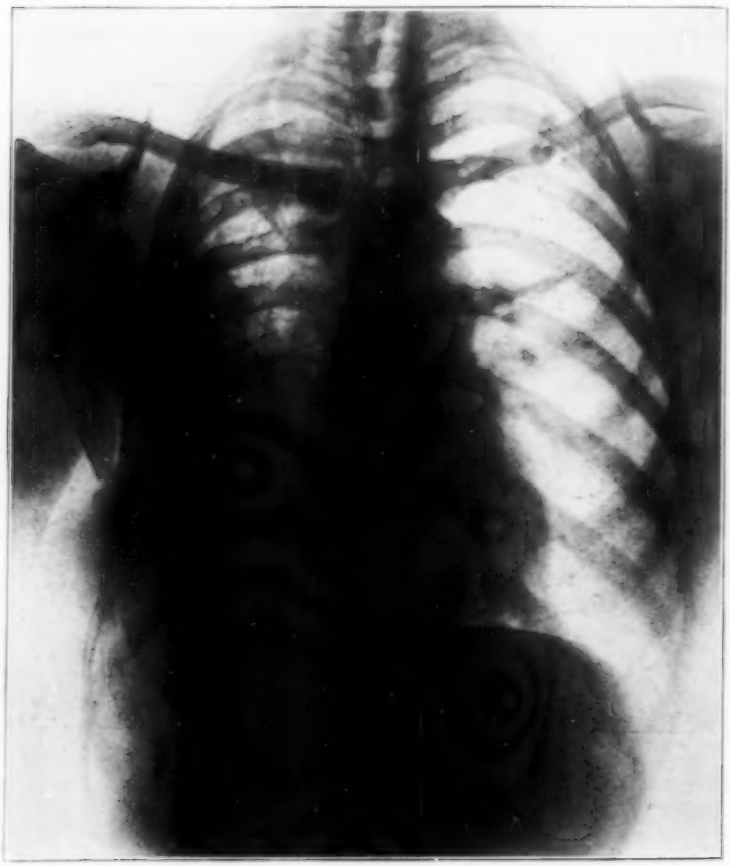

Fig. 4 (Case 4).—An extensive calcification of the right pleura extending from the second rib in front to the base and horizontally to the posterior axillary line. There are definite calcium deposits in the upper part of each lung. This patient expectorated more than forty small irregular calcium concretions during a recent attack of bronchitis.

REPORT OF CASES

Case 1.—Miss K., 38 years old, a graduate nurse, gave a history of questionable typhoid at the age of 25 years, and, for the last six years, intermittent

attacks of cough and slight fever accompanied by expectoration of numerous gravel-like substances which proved to be lime salts deposits. These deposits varied in size from that of fine sand to that of large peas. During the interval between the attacks, which seldom lasted more than a week, the patient was troubled with a slight bronchitis. She was sent to me during one of these attacks, and the following notations were made:

There was definite goiter of long standing, but no evidence of hyperthyroidism; the basal metabolism was plus 6; nutrition and development were normal. She had a severe cough followed by the expulsion at intervals of small calcareous granules, irregular in formation. There were no acid-fast

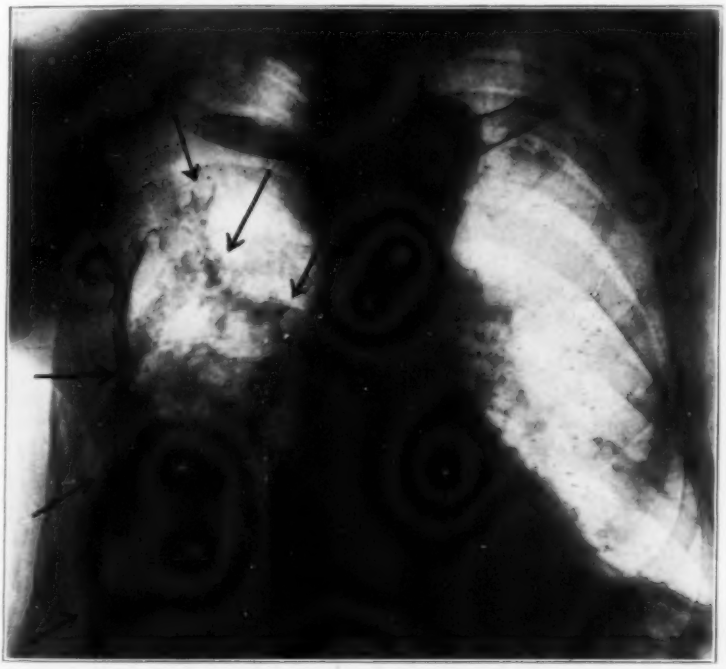

Fig. 5 (Case 5).—An extensive calcification of the right pleura showing a definite compression of the lung tissue. The patient was 83 years of age and gave a history of pneumonia and empyema fifty-nine years ago. He has enjoyed reasonably good health ever since.

bacilli in the sputum. There was slightly impaired resonance over each lung root in front, with increased intensified voice sounds and a few fine râles in the left interscapular region.

The stereoroentgenograms (Fig. 1) showed a peculiar round, mulberry-shaped shadow below the inner half of the right clavicle in the upper lung root zone. The contents suggested an irregular mass of calcareous degeneration. The mass had the appearance of a large calcareous gland which communicated with some of the larger bronchi and was the source of the "lung stones" expectorated at intervals.

It is now eight years since we made this examination, and since then we have repeated the investigation each year, sometimes three and four times a year. Many stereoroentgenograms of the chest were secured and they have shown this gland or sac entirely empty on one occasion; other times, at varying degrees of fulness, from a few pebbles to the completely filled sac, such as is shown in Figure 1. The patient has continued her vocation during these years, and, except for an occasional attack of "lung stones," has enjoyed good health. It has never been proved that the patient had a manifest pulmonary tuberculosis, although it is reasonable to believe that a tuberculous bronchial adenitis was the initial cause of the subsequent calcareous degeneration.

Fig. 6 (Case 6).—The shadow in the right thorax is an organized mass (probably an organized hematoma) with a shell of calcareous deposits. Twelve years ago, the patient was accidentally shot in the right clavicle. The bullet traveled downward traversing the pleura and lodging below the right diaphragm.

Case 2.—Mrs. M. W., aged 49, had a severe bronchitis three years ago. She has no present respiratory symptoms.

Both physical and fluoroscopic examinations were negative. The stereoroentgenograms (Fig. 2) showed a shadow similar to that described in Case 1 (Fig. 1), characteristic of a calcareous mass the size of a walnut and corresponding in position to a bronchial gland (Fig. 2). In this case, unlike Case 1, there was no history of the expectoration of "lung stones." Four years later this patient was reexamined and similar findings were noted.

Case 3.—Mrs. U. W., shown in Figure 3, had practically the same type of case as the patient in Case 2. There were no respiratory symptoms and no history of any past respiratory disturbances; the patient was in normal health, and the enlarged calcareous glandular mass caused no symptoms.

Case 4.—Mrs. C. J. was referred to my medical division with the following history: At the age of 18 she had an attack of what was called typhoid, although no abdominal symptoms were present; no other similar cases occurred in the neighborhood at the time. This attack was followed by some acute respiratory symptoms, with fever and pain in the lower right thorax. Since then she had not been strong and had taken good care of herself, thinking she had weak lungs, although physicians would not say she had tuberculosis.

Fig. 7 (Case 6).—This illustration shows the bullet lodged in the muscles of the posterior abdominal region of the right side.

Recently a slight dyspnea and a wheezing within the chest had been frequent and disturbing symptoms. The patient had seldom been free from a slight cough and expectoration, but tubercle bacilli had never been found in the sputum.

Examination showed a slightly enlarged thyroid, no tremor; she was fairly well nourished; the right clavicle was prominent; there was extreme retraction of the entire right thorax with immobility; Krönig's isthmus was nearly obliterated; there was decreased resonance over the lower two thirds of the right thorax, associated with feeble breath sounds and increased whispered voice sounds; harsh breath sounds were found below the left clavicle.

The stereoroentgenograms of the chest (Fig. 4) revealed a definite retraction of the right thorax, intensified at the base, and an extensive thickening of the pleura, with the density typical of calcareous degeneration. This thickness

began at the second rib in front and extended as low as the sixth; it was about 4 inches (10.16 cm.) wide and held the lung in slight collapse. In the upper third of both lungs, there were some large calcareous deposits the size of beans. The right oblique chest plate showed no abnormal thickness or widening of the descending aorta.

The patient was referred to me two months later on account of severe cough and expectoration, the latter containing "lung stones" varying in size from small shot to a small pea, irregular in shape and rough in contour. This attack lasted three or four days, and during this time between forty and fifty of these calcareous substances were expectorated. On analysis, calcium carbonate proved to be the chief ingredient, with about 6 per cent. organic matter, probably dried mucus. There were 9.3 gm. of blood calcium in 100 c.c. of blood. The Wassermann test was negative. The intracutaneous tuberculin test gave a moderate reaction in twenty-four hours. A physical examination of the chest at this time revealed many medium sized râles, increased on coughing under the right clavicle to the fourth rib; in the suprascapular region, a similar condition was found on auscultation. It is our opinion that the disintegration of calcium deposits comes from the right thorax on account of the definite changes in the physical findings in two months' time.

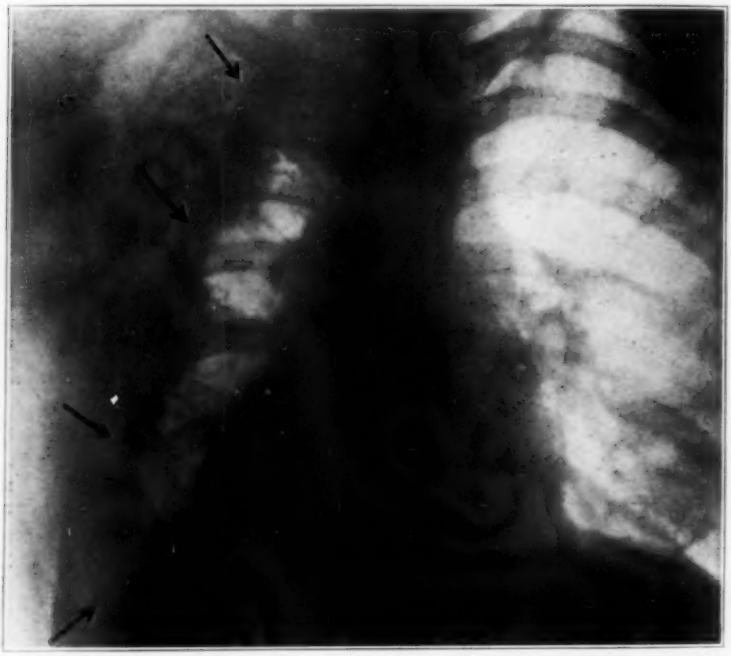

Fig. 8 (Case 7).—The left lung is partially collapsed, and the pleura shows a dense fibrocalcareous thickening extending from the clavicle to the base. The patient sought advice on account of hypertension. There were no respiratory symptoms. A severe pleurisy in childhood was the only serious illness complained of.

The diagnosis was obsolete pulmonary tuberculosis, with extensive calcification of the right pleura and some calcareous degeneration in both upper pulmonary lobes.

CASE 5.—Mr. A., aged 83, sought help on account of a cough which had troubled him for three winters, but which disappeared during the summer months. A small amount of mucoid sputum accompanied the cough; dyspnea was not a prominent symptom, considering the patient's age. No acid-fast bacilli were found on frequent examinations of the sputum.

Fig. 9 (Case 8).—This illustration shows an extensive calcified pleura in the form of a shell encasing the right lung. This patient had a severe and prolonged attack of pleurisy at the corresponding base forty years ago—a probable empyema following aspiration as the patient was confined to bed for four months following the latter.

The physical examination of the chest showed immobility of the right lower thorax and decidedly impaired resonance over the lower two thirds of the right lung. Auscultatory sounds were absent at the base, front and back; there were feeble breath sounds above the seventh rib in the back and the third rib in front; also a few fine râles at the base of the left lung in the axillary region.

In the stereoroentgenograms of the chest (Fig. 5), a dense shadow was seen over the lower two thirds of the right lung, characteristic of a massive

shell of thickened pleura. The plates gave the suggestion of a lung encased in a cement jacket extending around the entire lower part of the lung.

The patient was given digitalis, and the cough slowly disappeared. It is now three years since we first observed this case, and the administration of digitalis each fall relieves the winter cough. The early history of this patient is interesting. During the Civil War, he enlisted in an infantry company and, after taking a forced march during a cold rain, was compelled to rest without shelter. Three days later, the patient was in the army hospital with a severe pneumonia of the base of the right lung. Convalescence was interrupted by a severe relapse six weeks later, which was followed by two years of invalidism

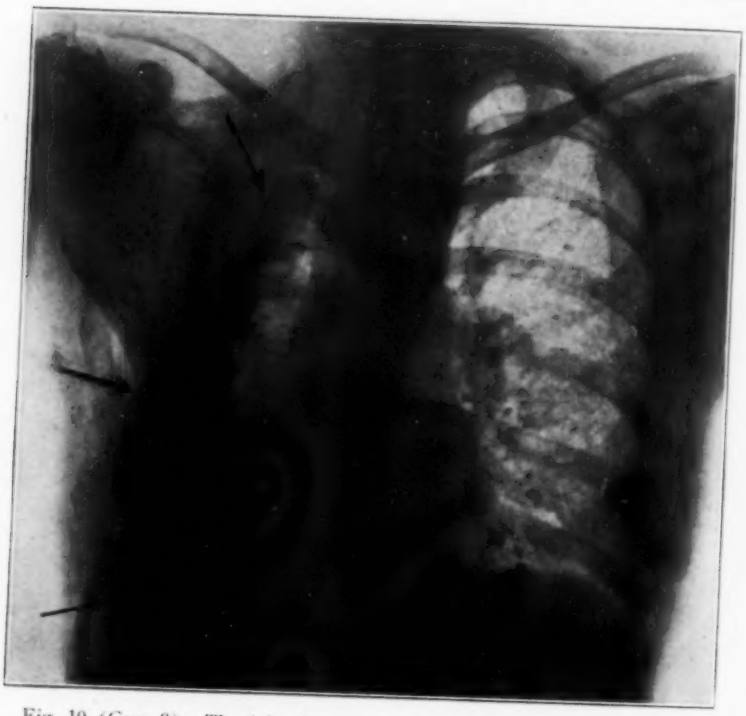

Fig. 10 (Case 9).—The left pleura shows a massive cement-like formation in the form of a large sheet of calcareous degeneration, marking the seat of a severe empyema fourteen years ago.

in the army hospital. During this time, the army surgeons used frequent cupping of the right lung to promote resolution. It was four years before the patient was able to work. In all probability, the present extensive calcification at the base of the right lung is the terminal result of pneumonia followed by empyema about fifty-nine years ago.

Case 6.—Twelve years ago, Mr. H. E. S., aged 32, was accidentally shot in the right superclavicular region with a .32 caliber bullet, which traveled downward, penetrating the right diaphragm and lodging in the abdomen. The patient was in bed for twenty-six weeks with cough and symptoms of lung

trouble, but recovered and has had no recurrence since. He sought treatment for gastrointestinal disturbances.

The physical examination of the chest revealed dulness from the clavicle to the base in the front of the right lung. Feeble breath sounds were present over the lower two thirds of the lung in the back. Stereoroentgenograms showed an extensive mass filling the pleural cavity, with a distinct calcified shell surrounding the mass (Fig. 6). In all probability, the bullet (Fig. 7) in its downward course caused an extensive hematoma, which afterward formed an organized mass with the deposit of calcium salts forming the outer border.

Case 7.—Mr. C. C. H., now aged 51, at the age of 16 was sick in bed for two weeks with a severe attack of pleurisy followed by two months of indisposition; at the age of 33, he had a severe attack of mumps, making a rapid recovery. Slight dyspnea had been a persistent symptom for years.

Physical examination of the chest showed the right lung to be clear. The left lung showed dulness from the clavicle to the base, with a great deal of

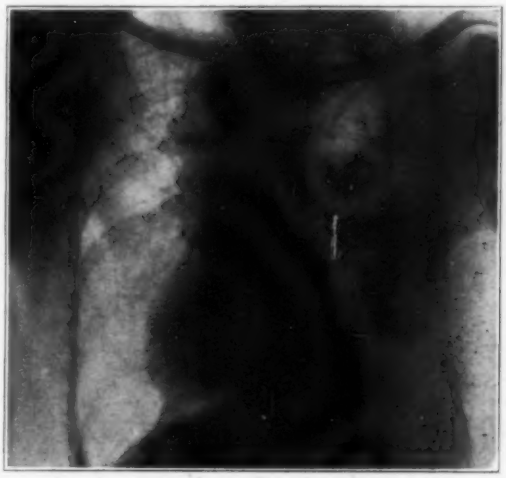

Fig. 11 (Case 10).—This case is similar to that portrayed in Figure 10, except that the empyema occurred forty-three years ago.

retraction of the entire lung. Breath sounds were feeble. There were few crepitations in the first and second interspaces external to the midclavicular line. In the back, decreased resonance was found over the entire surface, more intense from the sixth rib to the base. On auscultation feeble breath sounds and fine crepitations were heard at the base.

Stereoroentgenograms of the chest (Fig. 8) revealed a long strip of fibrocalcareous tissue running from the clavicle to the base of the left lung. It is located about the outer third of the thoracic cavity and is about 2 or 3 cm. in thickness, as viewed from the posterior-anterior position.

Case 8.—Mrs. H. G., aged 61, consulted a physician on account of symptoms characteristic of some circulatory disturbance. The history stated that forty years before, the patient had had a severe attack of pleurisy at the right pulmonary base, which necessitated the aspirating of considerable fluid. This illness kept the patient confined to bed for about four months with a moderate fever, cough and weakness. Later a sea voyage seemed to benefit her greatly.

For a number of years following this illness she was not considered strong, but she was free from any respiratory symptoms until about four years ago, when an unproductive cough developed, which in the light of the present examination could be attributed to the circulatory deficiency in the form of an aortic aneurysm (Fig. 9).

Physical examination of the chest revealed extensive retraction of the right side with definite decreased resonance over the lower two thirds of the pulmonary area. Coarse râles and rhonchi were heard below the corresponding clavicle to the fourth rib.

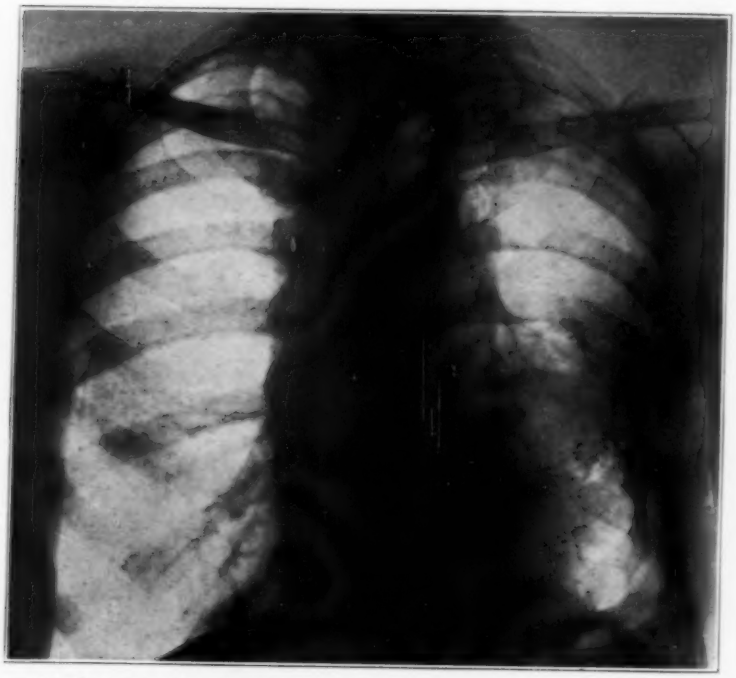

Fig. 12 (Case 11).—An isolated calcareous plaque in the left pleura of a man 75 years old. The history of severe malaria at the age of 20 was the only suggestive evidence of pneumonia or empyema.

Stereoroentgenograms of the chest (Fig. 9) showed that the entire mediastinum was pulled to the right. There was a manifest aortic aneurysm, and the right lung was encased in a hard shell-like substance characteristic of an extensive deposit of lime salts at the seat of the pleuritis forty years before. The blood Wassermann test was negative. No acid-fast bacilli were found in the sputum.

Cases 9 and 10.—These patients had practically the same history as in the preceding case in that the patients had not suffered from any recent chronic respiratory ailment, but a definite empyema apparently existed years prior to the present investigation. In Case 9 there was massive cementing of the entire left pleura (Fig. 10) in the form of a large sheet of calcareous degeneration.

This patient had had severe pneumonia followed by empyema fourteen years before. The patient in Case 10 was suffering from a definite myocardial degeneration; the extensive calcified patch (Fig. 11) involving most of the right pleura was, in all probability, the result of a pneumonia followed by empyema forty-three years before.

CASE 11.—Figure 12 represents a calcareous plaque in the left pleura of a man, 75 years of age, with no definite history of pneumonia or empyema,

Fig. 13 (Case 12).—The extensive calcification seen in the cervical glands in such uniform arrangement is unusual. The patient had what is reasonable to consider a chronic cervical adenitis (tuberculous) in early adult life. A substernal goiter is apparent.

except that at 20 years of age a severe attack of malaria (?) kept the patient in bed for three weeks. This isolated patch of pleural calcification is rather frequently found since the advent of the roentgen ray.

CASE 12.—The case of Mrs. Mc. is most interesting in that the history reveals distinct evidence of a definite cervical adenitis in early adult life when the glands would become enlarged and tender for weeks at a time, and this

condition was always associated with a definite fatigue and ill health. The patient's mother died of pulmonary tuberculosis; two brothers died in their twenties of the same disease. The patient, who is now 50 years of age, had never been strong. She had always been underweight and nervous; she had acute nephritis after her second pregnancy; for a few years after this a cough persisted which was always considered bronchitis. The present symptoms and indisposition may be reasonably attributed to hypertension. The Wassermann test was negative. There were no respiratory symptoms. Stereoroentgenograms of the chest and cervical region (Fig. 13) plainly showed an extensive calcification of the complete chain of cervical glands; the anterior and posterior

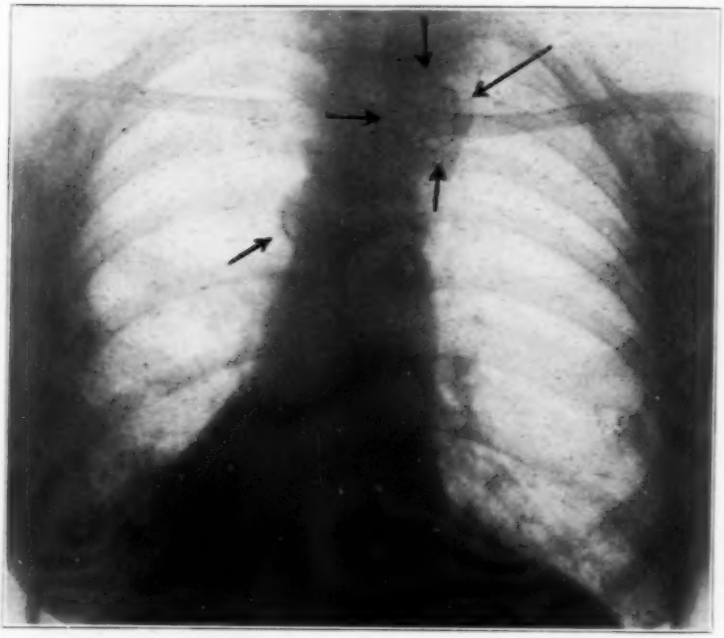

Fig. 14 (Case 13).—A definite substernal goiter in this case shows a deposit of lime salts in the right side. It is unusual in that the calcification is entirely confined to the substernal portion of the goiter.

divisions were easily recognized. The history and roentgen-ray evidence mark this as a rather definite case of an obsolete tuberculous cervical adenitis followed by calcification.

Case 13.—Mrs. S. K., aged 52, gave a history of bronchopneumonia fourteen years before. She had never been strong and had had hemoptysis at the age of 20; seventeen years ago she had had a severe attack of coughing and spat blood; she had had influenza three years ago, and a persistent cough had been the sequence.

Physical examination of the chest showed an enlarged thyroid, particularly on the right, extending downward to the suprasternal notch. There was definite pulsation over this enlargement.

Stereoroentgenograms of the chest (Fig. 14) showed an extensive substernal goiter, running down to the aortic arch, more enlarged on the right than on the left; and in this enlargement there was a large calcareous mass as big as a hickory nut, in the substance of the substernal goiter, opposite and below the inner end of the right clavicle. There was a smaller calcareous deposit, about half the size of the one on the left, in the right thyroid area, but this was above the suprasternal notch. The trachea was pushed toward the left. The heart was normal in size, but the aortic arch had a plaque of calcareous deposit, showing an atheromatous condition. The descending aorta

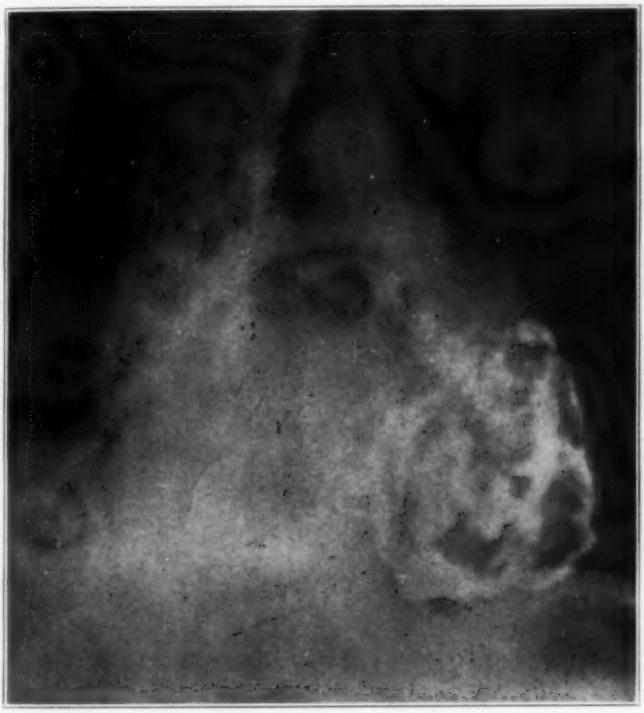

Fig. 15 (Case 14).—Extensive calcification of the pericardium in a woman, associated with cirrhosis of the liver and ascites. (Reported by Dr. J. T. Case: J. A. M. A. **80**:236 [Jan. 27] 1923.)

was distinctly widened in the form of a fusiform dilatation. The unproductive cough may be due to pressure of the calcified mass in the substernal goiter.

Case 14.[50]—Mrs. Z. R. was apparently in good health until two years ago, when she slowly developed circulatory disturbances and later abdominal ascites.

The roentgen-ray chest plates (Fig. 15) revealed a peculiar condition of the heart. In the left border, there was a semilunar calcified ring which appeared to be the result of some old pericarditis or diaphragmatic pleurisy. This cal-

50. Case, J. T.: Pericarditis Calculosa: Report of a New Case Discovered Roentgenologically, J. A. M. A. **80**:236 (Jan. 27) 1923.

cification was in the pericardium. A left oblique pair of stereoroentgenograms showed that this circular patch was situated in front of the anterior cardiac wall. It gave the appearance of an extensive irregular calcified patch about 8 cm. in every diameter, ovoid and flat in appearance.

The physical examination showed decreased resonance over the back of both lungs in the lower half, accompanied by medium sized râles suggesting a chronic venous congestion.

Case 15.—Mrs. J., aged 51, complained of an intermittent diarrhea of many years' duration. A year ago an exploratory laparotomy failed to reveal any cause of the dysentery. A carefully taken history did not elicit the existence

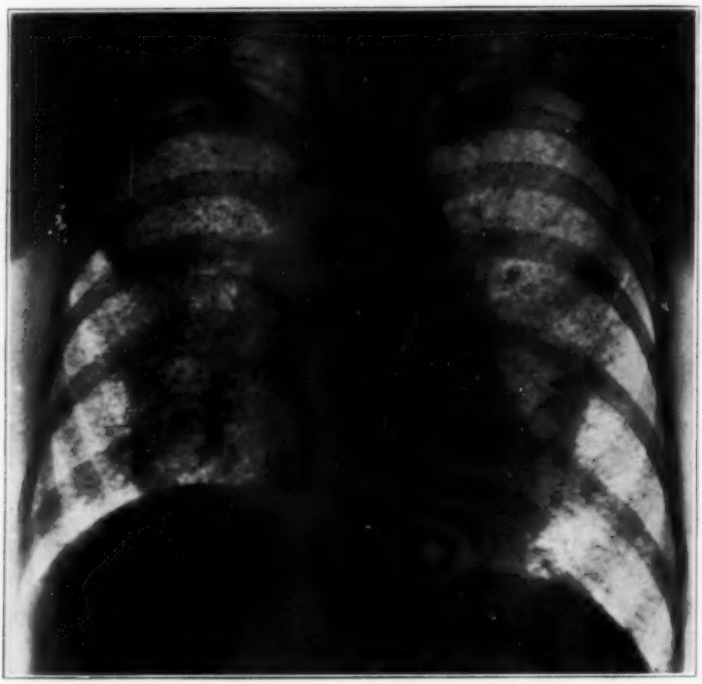

Fig. 16 (Case 15).—An apparent calcareous metastasis in a woman of 51 years. There was no history of respiratory disease or chronic osseous affections. Seven years later stereoroentgenograms gave the same appearance. The Wassermann test was negative.

of any present or past chronic respiratory disorder. Physical examination of the chest showed little or no abnormality.

Stereoroentgenograms of the chest (Fig. 16) give a dramatic picture in the form of a complete and evenly distributed peppering of the whole pulmonary field with small shot-like, clean-cut deposits characteristic of calcification metastasis. No history of disease of the osseous tissue was obtained. Seven years later the patient returned and the stereoroentgenograms of the chest showed the same appearance. The Wassermann test was negative on both occasions.

OBSERVATIONS ON SALT IN VASCULAR HYPERTENSION *

JAMES P. O'HARE, M.D.
AND
WILLIAM G. WALKER, M.D.
BOSTON

Any therapeutic measure claiming efficacy in a given disease or condition should fulfil at least this primary condition: It should be proved beyond a reasonable doubt that this measure, and this alone, produced the given result. As a corollary to the main proposition, it may be fairly demanded that any maneuver claiming to be more effective than another should show that the former measure is definitely and measurably superior to the latter.

In 1920, Allen [1] published a paper in which he asserted that a greater restriction in salt intake in cases of hypertension would produce a much greater reduction in pressure, a greater relief in symptoms, a speedier clearing up of retinal hemorrhages, etc., without other restriction in diet, exercise, etc., than other methods of treatment. He advocated limiting the intake of salt to 0.5 gm. a day instead of the usual 2 gm. His claim, if true, would have been a welcome advance in our therapy of a troublesome and apparently increasing disease.

This seemed, however, rather hard to believe for several reasons. In the first place, there is no good foundation for the restriction of salt in cases of hypertension with the exception of those associated with nephritic retention. The only reason given for the almost universal restriction of salt in treating hypertension is based on the assumed decreased viscosity of the blood resulting therefrom. But this is mere assumption and not proved or accepted. Perhaps the close relation between chronic nephritis (with salt retention) and vascular hypertension is responsible for the salt reduction treatment. Perhaps, it is pure empiricism or a clever method to prevent overeating by rendering the food less palatable.

In the second place, it was hard to believe that a reduction in salt intake from 2 gm. to 0.5 gm. would prove so much more effective than the restriction from 10 gm. to 2 gm., as had been tried frequently.

Then, too, it seemed hard to understand the comparatively low pressure of subacute nephritis and chronic nephritis with edema. Only

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* From the Medical Clinic of the Peter Bent Brigham Hospital.

* This paper was read by title at the meeting of the American Society for Clinical Investigation in Washington, May, 1922.

* This paper is the second one of a series of studies in metabolism from the Harvard Medical School and allied hospitals. The expenses of this investigation have been defrayed in part by a grant from the Proctor Fund of the Harvard Medical School for the Study of Chronic Diseases.

1. Allen, F. M.: Arterial Hypertension, J. A. M. A. **74**:652 (March 6) 1920.

rarely is hypertension seen in these conditions, and yet they show the greatest retention of salt.

Furthermore, if the salt is such a determining factor, we should expect to find the blood chlorid increased in our hypertension cases and a definite relation existing between the level of this substance and that of the blood pressure. Charts 1, 2 and 3 throw some light on this subject.

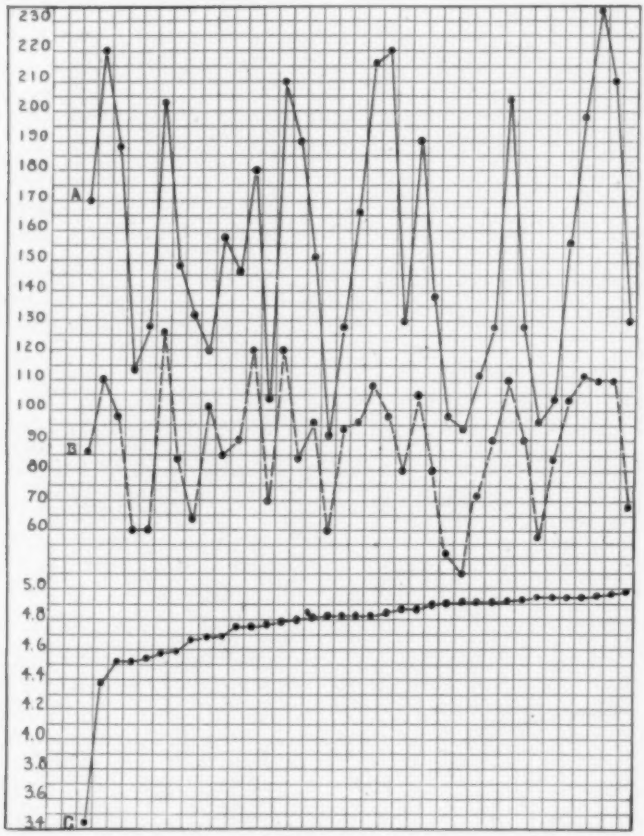

Chart 1.—Thirty-seven determinations of blood pressure and whole blood chlorid on thirty-three patients. Pressure and chlorid determined on the same day. Twenty of the thirty-seven had hypertension. The arrangement is according to an ascending value of the blood chlorid. All of these except the lowest are within the accepted limits of normal. The commonly accepted limits for normal according to Myers, McLean and Berglund are 4 to 5 gm. per liter of whole blood and 5.62-6.25 gm. per liter of plasma. Berglund feels that even 5.2 gm. per liter of whole blood is normal. In the chart, *A* represents systolic blood pressure; *B* diastolic blood pressure; *C* whole blood chlorid in grams per liter.

BLOOD PRESSURE AND WHOLE BLOOD CHLORIDS IN THIRTY-THREE PATIENTS

Chart 1 demonstrates some significant facts. Although none of the blood chlorids is above normal, twenty of the thirty-seven pressures are above normal. Eight patients had systolic pressures of over 200 and three had diastolic pressures of 120 or over. More significant even

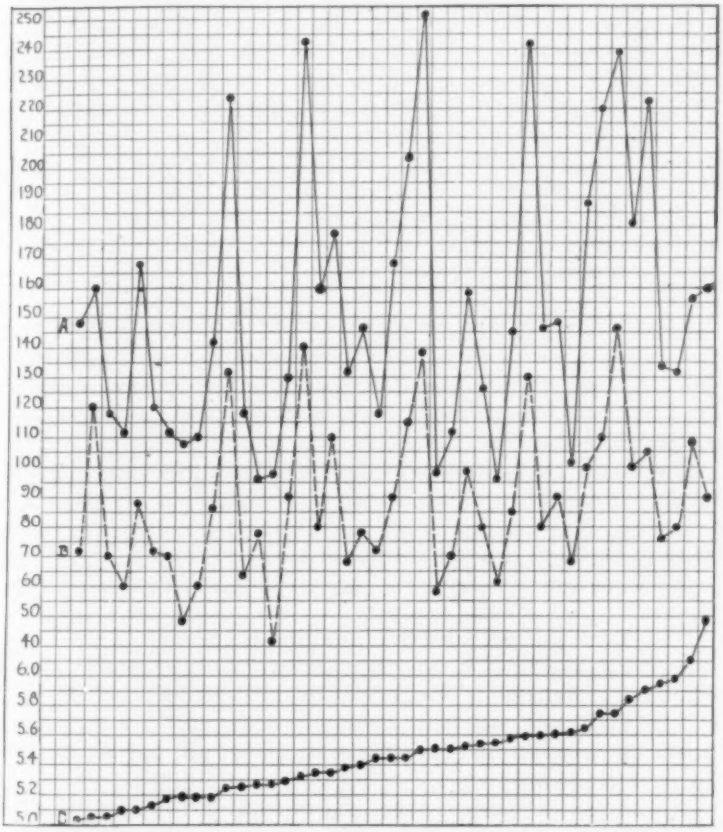

Chart. 2.—Forty-three determinations on twenty-four patients. Twenty-three had hypertension. Arrangement is the same as in Chart 1. *A* represents systolic blood pressure; *B*, diastolic blood pressure; *C*, whole blood chlorid in grams per liter. The whole blood chlorids are all above normal.

is the contrast between the curve representing the blood chlorids and those of the pressures. The pressures are represented by absolutely irregular types of curves without any relation to the blood chlorid curve,

which steadily climbs. High systolic and diastolic pressures may be found corresponding to low values of chlorid and normal or low pressures associated with the higher chlorids in this chart. The chart demonstrates that hypertension is compatible with normal or low blood chlorid, and that there is no relation between the levels of the chlorid and the pressures.

Chart 2 is similar to Chart 1. However, all of the blood chlorids in this chart are above normal. Despite this fact, twenty of the forty-three pressures are normal or low. The contrast between the steadily rising curve of the blood chlorids and the absolutely irregular, jagged curves of the pressures is as marked as in Chart 1. It may be pointed out that there are many higher pressures, both systolic and diastolic, in this group than in the one preceding. On the other hand, there are many lower. In our first chart, there are only two systolic pressures as low as 120, whereas in the second chart there are fourteen. Chart 2 indicates that a normal or low blood pressure is compatible with a high blood salt content, and that there is no relation between the levels of chlorid and pressure.

BLOOD PRESSURE AND BLOOD PLASMA CHLORIDS IN VASCULAR HYPERTENSION

Chart 3 illustrates the facts brought out in the two previous ones. The single high plasma chlorid in so many patients with hypertension is especially noteworthy.

These three charts demonstrate that in different persons: (1) hypertension is compatible with normal blood chlorid; (2) normal tension is compatible with high blood chlorid; (3) there is no relation between the height of the blood pressure and that of the blood chlorid.

Such conclusions apply also to the same determinations in the same patient.

The figures in Table 1 speak for themselves and indicate that in the same patient, as well as in different patients, there is absolutely no relation between the level of the plasma chlorid and the blood pressure. In the fourth, fifth and sixth patients in this group, it is interesting to note the pressures corresponding to the lowest and highest chlorids. They are almost alike.

Another doubt is cast on the relation between the blood pressure and the chlorid metabolism. It seems difficult to imagine that changes in the salt metabolism of the body could take place rapidly enough to bring about the sudden and often marked changes that take place in the blood pressure from second to second and from minute to minute.[2]

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2. O'Hare, J. P.: Vascular Reactions in Vascular Hypertension, Am. J. M. Sc. **159**:369, 1920. Common Sense in the Interpretation of Hypertension, Clin. North America, **5**:1349, 1922.

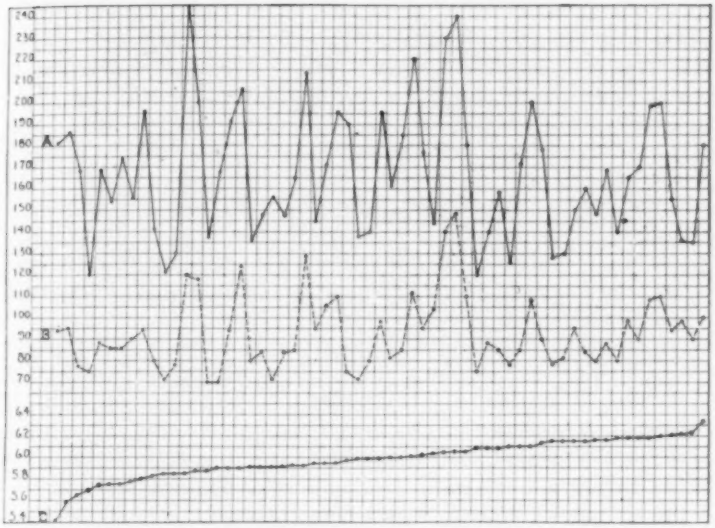

Chart. 3.—Sixty-one determinations of blood pressure and plasma chlorids on thirteen patients. All cases but the first have been diagnosed as vascular hypertension, although seventeen at the time showed a normal pressure. The plasma chlorids are all within the accepted limits of normal, except the first two which are low, and the last which is high. The arrangement is the same as in Chart 1. *A* represents systolic blood pressure; *B*, diastolic blood pressure; *C*, plasma chlorid in grams per liter.

TABLE 1.—*Cases in Which Plasma Chlorids and Blood Pressures Have Been Repeated*

Medical No.	Plasma Chlorid	Blood Pressure		Medical No.	Plasma Chlorid	Blood Pressure	
		Systolic	Diastolic			Systolic	Diastolic
12,459	5.83	142	80	15,402	5.91	156	72
	5.85	122	72		5.91	148	84
	5.86	130	78		5.93	165	85
	5.89	138	70		5.96	196	110
	5.99	138	72		5.99	140	80
	6.09	120	75		6.00	162	82
	6.18	140	80		6.10	172	85
	6.14	178	90		6.18	165	98
	6.15	150	95		6.20	200	110
	6.18	170	90				
				15,811	5.95	145	99
17,285	5.41	182	94		6.04	144	104
	5.58	186	95		6.06	180	110
	5.65	168	78		6.15	128	78
	5.75	168	88		6.23	136	98
	5.76	174	86		6.24	136	90
	5.76	154	86				
	5.78	156	90	17,477	5.86	244	120
	5.80	196	94		5.88	200	118
	5.91	136	80		5.90	206	124
	5.99	196	98		5.93	214	128
	6.01	220	112		6.05	230	140
	6.09	140	88		6.06	240	148
	6.00	158	86				
	6.10	126	78	16,202	6.03	177	95
	6.15	130	82		6.16	168	88
	6.15	100	84		6.16	148	80
					6.18	198	108
					6.21	155	94
					6.34	180	100

TABLE 2.—*Effect of Alternate Low Salt and Higher Salt Intake*

Case	Period	Duration in Days	Systolic and Diastolic Pressures at Onset	Highest Systolic Pressure	Lowest Systolic Pressure	Variation in Systolic Pressure	Average Systolic Pressure	Difference in Average Systolic Pressure	Highest Diastolic Pressure	Lowest Diastolic Pressure	Variation in Diastolic Pressure	Average Diastolic Pressure	Difference in Average Diastolic Pressure
1	0.5	16	190/100	195	140	55	168	+14	110	80	30	92	+3
	4.0	18	145/ 85	185	135	50	154		100	75	25	89	
2	4.0	9	124/ 64	130	124	6	127	+12	70	64	6	67	+10
	0.5	15	134/ 66	150	122	28	139		88	64	24	77	
3	0.5	8	180/110	180	120	60	137	+9	110	80	30	88	+2
	4.0	7	165/ 80	140	105	35	126		90	80	10	86	
4	0.5	15	204/110	208	173	35	193	+3	106	92	14	99	0
	4.0	15	182/ 94	220	174	46	190		112	90	22	99	
	0.5	64	196/ 98	196	136	60	165	(25)	106	78	28	84	15
5	0.5	13	168/ 60	172	156	16	165	0	70	58	12	64	+2
	4.0	8	158/ 54	174	156	18	165		70	54	16	60	
	0.5	11	162/ 60	170	152	18	159	(6)	70	56	14	63	+3
6	4.0	10	150/ 78	150	134	16	141	1	83	64	19	73	+5
	0.5	12	138/ 74	152	128	24	140		84	68	16	78	
7	4.0	6	230/140	266	230	36	247	1	148	130	18	142	10
	0.5	38	254/150	256	192	64	246		164	122	42	132	
8	0.5	16	178/ 94	200	140	60	162	4	98	74	24	88	+2
	4.0	15	162/ 82	180	156	24	166		98	80	18	86	
	0.5	15	168/ 88	182	148	34	164	(2)	102	72	30	89	+3
9	4.0	7	188/135	188	160	28	175	5	135	110	25	124	13
	0.5	25	153/110	200	150	50	170		132	104	28	111	
10	4.0	8	200/130	220	195	25	204	7	155	125	30	131	3
	0.5	18	220/140	220	170	50	197		140	105	35	129	
11	4.0	15	225/ 95	255	215	40	229	11	110	85	25	98	4
	0.5	31	225/100	243	140	103	218		120	70	50	94	
	4.0	18	215/ 85	240	200	40	218	(0)	110	85	25	90	+4
12	4.0	9	214/130	214	180	34	201	13	120	105	25	119	5
	0.5	20	198/110	202	160	42	188		120	94	26	114	
13	4.0	7	170/ 90	205	162	43	185	18	105	80	25	91	0
	0.5	46	178/ 90	195	145	50	167		105	80	25	91	
14	4.0	8	180/ 90	210	180	30	194	19	120	90	30	106	14
	0.5	38	185/ 95	260	135	125	175		140	75	65	92	
15	4.0	8	193/ 98	220	150	70	200	22	110	80	30	99	0
	0.5	14	212/100	215	150	65	178		110	90	20	99	
16	4.0	13	250/130	250	220	30	234	22	142	116	26	129	10
	0.5	11	228/114	232	194	38	212		138	108	30	119	
17	4.0	6	206/100	244	206	38	233	24	130	100	30	118	16
	0.5	22	224/122	224	190	34	209		112	90	22	102	
18	4.0	10	200/122	240	185	55	205	40	150	105	45	126	19
	0.5	35	198/118	220	132	88	165		140	90	50	107	
	10.0	6	148/ 90	184	145	39	161	(+4)	110	90	20	106	+1

It is hard to believe that the salt has anything to do with such a marked change in pressure in such a short period of time as is illustrated in Chart 9. Note particularly the change of over 100 mm. systolic and 55 mm. diastolic pressure in twenty-four hours on March 1. Such a tremendous change, one would feel, must assume an equivalent change in chlorid metabolism. The urine and plasma chlorids indicate no such change. Furthermore, we know that any such marked change would be extremely dangerous to life. It is certain in this case that nervous influences were responsible, and it is hard to believe that these act on the vessels through sudden changes in salt metabolism.

In spite of the doubts that crept into our mind, it seemed desirable to check up the very low salt regimen to discover whether it fulfilled the requirements mentioned in the introduction of this paper. At first thought this might seem a simple, straightforward piece of work. Our original plan was to place patients with hypertension, on alternate weeks, on a 0.5 gm. and 4 gm. salt regimen. Many practical difficulties were soon encountered. The chief of these was our inability to get, in one week, dechloridization sufficient to bring the case within the accepted limits of an excretion of salt of 0.5 gm. or less a day. This necessitated, as a rule, the use of long periods of low salt intake and shorter control periods. Rarely could our patients stay in the hospital long enough to allow a period of higher salt intake comparable in length to the low salt period. This time variable should be borne in mind in the interpretation of the results.

Since the reduction in pressure was the only measurable criterion, we felt that we should use cases of pure hypertension and exclude those complicated by nephritis. Eighteen cases of vascular hypertension, therefore, were selected. Our aim was to have these patients under as constant conditions as possible during the experiment. They were, therefore, all kept at rest in bed during the entire period of observation. All were given a fixed diet containing 60 gm. of protein, 2,000 calories, and 1,800 c.c. of fluid. The only (controllable) variation was in the salt intake, which was alternately 0.5 gm. and 4 gm. (The latter amount was selected instead of 2 gm. to exaggerate any differences due to the low salt content.) Practically the only variable over which we had no control was nervous influences. These played, however, an important part.

Blood pressure readings were taken at the same time each day. The chlorid in the urine was quantitated daily to control the intake. The plasma chlorid was determined, as a rule, once a week.

The only good way to view the results of this study is to see the charts. For obvious reasons, only a few can be included here. A table such as Table 2 is the most easily available way to present the data in print. Necessarily, it is somewhat imperfect.

The arrangement of patients is in order of differences in the average systolic pressures. A plus sign indicates that the pressure was lower with the 4 gm. than with the 0.5 gm. intake. In the first column is indicated the salt period—either 0.5 gm. or 4 gm. In the given case, the arrangement of the periods is chronologic. The second column indicates the duration of the periods in days. (It will be noted that the 0.5 gm. period is often considerably longer than the control period. It has, therefore, the added advantage of longer rest in bed, etc.) In the next column is given the systolic and diastolic pressures at the onset of the experiment. The next two columns contain the highest and lowest systolic pressures and the following one the difference between these two. These three give us the range of fluctuation. The next column

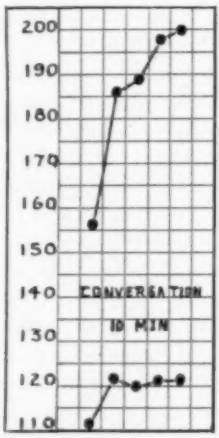

Chart. 4.—Effect of conversation. Pressures taken every two minutes.

gives us the average systolic pressure. The one following indicates the difference between the average systolic pressures in the periods. The remaining columns are the same for the diastolic pressure.

Before analyzing these figures in detail, let us see what previous experience with patients with hypertension has taught us. This will enable us to judge our results more correctly and to avoid the extremely common error of misinterpretation.

This experience has shown clearly that the pressure is extremely variable from minute to minute.[2] Systolic changes of 25 mm. to 40 mm. are not uncommon.

Chart 4 illustrates a striking effect of ordinary conversation in one of our nervous patients with hypertension. In her, the systolic pressure jumped 30 mm. within two minutes of the beginning of a simple conversation. In ten minutes, this pressure had climbed from 156 to 200.

Another fact brought out previously is that the pressures not infrequently fall materially (40 or more millimeters, systolic) without any special treatment except physical and mental rest. Note the decrease of 68 mm. and 56 mm. in systolic pressure and 48 mm. and 20 mm. in diastolic, in the first patient in Chart 5.

This patient was given no special treatment except rest in bed. The diet was "house diet," with no restrictions in salt. The second patient in this chart showed a drop of 35 mm. systolic and 25 mm. diastolic pressure, in spite of the fact that the patient was getting 4 gm. of salt.

If the 0.5 gm. salt regimen is effective, it seems to me that we should expect: (1) a definite decrease in the variations, and (2) a material lowering of the pressure, about which there can be no question. With regard to the second point, we think it is fair to demand an average decrease in systolic pressure of 25 mm. and, perhaps, somewhat less in the diastolic. Anything less is doubtful and can easily be accounted for by the physical rest or mental ease obtained.

Let us now return to Table 2. An analysis of the columns headed "Variation in Systolic" indicates that there were wider variations in both systolic and diastolic pressures during the 0.5 gm. regimen. Seventeen times during the low salt regimen, the degree of fluctuation was greater. It was less only four times and the same once. As for the diastolic pressure, the figures are about the same: greater fluctuation during the low salt regimen fifteen times, less six times and the same once. These are brought out better in the charts than in this table. Certainly the low salt regimen does not prevent the wide swings in pressure so common in these patients.

Analysis of the columns headed "Difference in Average Systolic" and "Difference in Average Diastolic" shows that only Cases 4 and 18 can reasonably be assumed to show sufficient change in pressure during the 0.5 gm. regimen to admit the possibility of the low salt ingestion being effective. While such is a possible interpretation, certain doubts are cast on the truth of such interpretation. In Case 4, it is only in the prolonged sixty-four day second period that the pressure fell so much. In the first low salt ingestion period, in which the duration was identical with the control period, there was actually a slight difference in favor of the latter. Furthermore, when this patient was allowed much larger amounts of salt, there was no evident relation between the pressure and the amount of salt excreted (see Chart VI). In Case 18, too, there is some doubt because on an intake of 10 gm. of salt per day for six days, this patient had an average systolic pressure that was actually 4 mm. less than during the low salt period. This table does not indicate that the 0.5 gm. intake is of greater value than the 4 gm. salt diet.

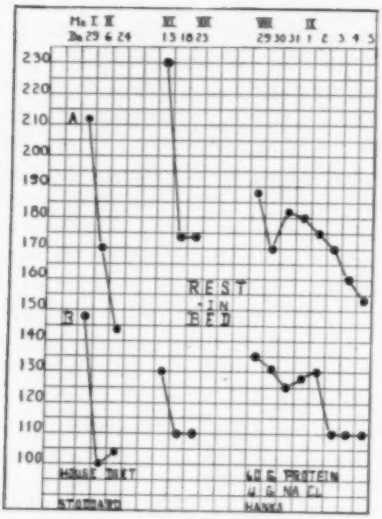

Chart 5.—Effect of rest in bed. At the top of the chart is indicated the month and just below it the day of the month. *A* represents systolic blood pressure; *B*, diastolic blood pressure.

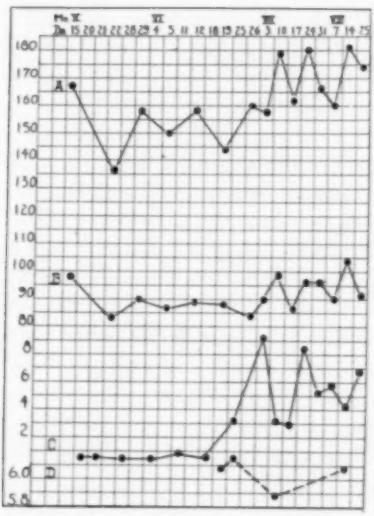

Chart 6.—Excerpt from the record of Case 4, illustrating the result of increased salt intake. *A* represents systolic blood pressure; *B*, diastolic blood pressure; *C*, twenty-four hour urine chlorid in grams; *D*, plasma chlorid in grams per liter.

Further evidence of the lack of relation between salt and hypertension is illustrated by four of our cases in which the patients took large amounts of salt, either at our suggestion or of their own free will. Case 18, Table 2, I have mentioned. This patient took 10 gm. of salt a day for six days. The table shows that during this period the fluctuations in pressure were less and the average pressures somewhat lower than during the 0.5 gm. salt regimen. Three more patients were

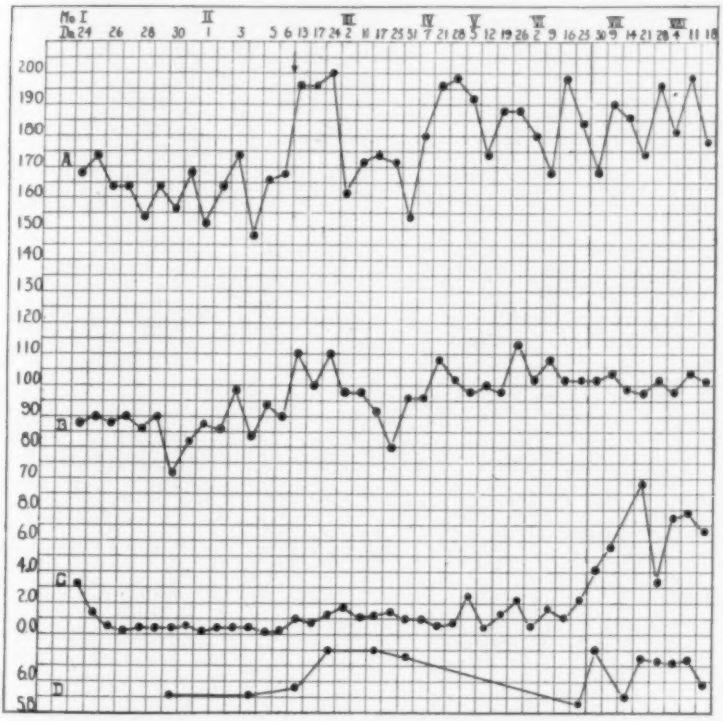

Chart 7.—Excerpt from record of Case 8. Patient discharged from hospital on February 7. *A* represents systolic blood pressure; *B*, diastolic blood pressure; *C*, twenty-four hour urine chlorid in grams; *D*, plasma chlorid in grams per liter.

followed after their discharge from the hospital, and the effect of increased salt ingested was noted.

It will be noted in Chart 6 that up to June 18 this patient was taking only enough salt to excrete less than 0.5 gm. After that date she took a greater and variable amount, as indicated by the urine chlorid. As one looks at the chart, the first impression is that with the increased salt intake, the pressure, especially the systolic, rose. However, a little

closer inspection of this period will show that while this is true, there is really no relation between the salt and the blood pressure. For, on July 3, the output of salt registered over 9 gm., and yet the blood pressure was the lowest in that period and just about what it had been in the 0.5 gm. period. On July 10, with a fall in the urine salt to 3 gm. and a fall also in the plasma chlorid, the systolic pressure rose 22 mm. and the diastolic 9 mm. Such observations make me feel certain that the general rise in pressure was due to factors other than salt.

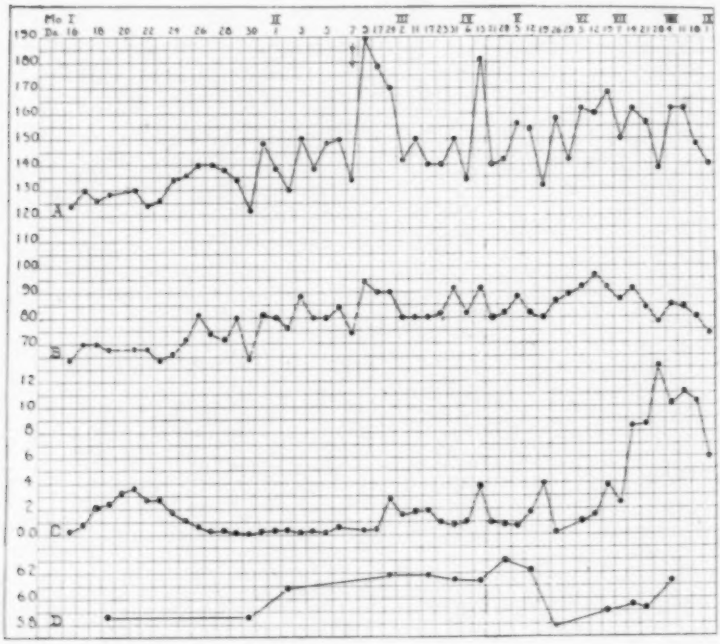

Chart 8.—Excerpt from record of Case 2. Patient discharged from the hospital on February 7. *A* represents systolic blood pressure; *B*, diastolic blood pressure; *C*, twenty-four hour urine chlorid in grams; *D*, plasma chlorid in grams per liter.

Case 8 is similar in many respects to the previous one. One may note in the chart that after the patient's discharge from the hospital and with her return to home conditions, there was a sharp rise in both systolic and diastolic pressure. There is no comparable change in salt excretion, which shows only a slight rise. It is not possible to believe that the latter had anything to do with the rise in pressure. If so, why should the latter continue to stay at approximately the same level when the salt excretion rose subsequently to seven or eight times its former

level? A point brought out in the previous chart is illustrated again here. On July 21, this patient's salt output was almost 10 gm., and yet the systolic pressure was much lower than on several other days when the excretion was between 0.5 gm. and 1 gm. On July 28, a

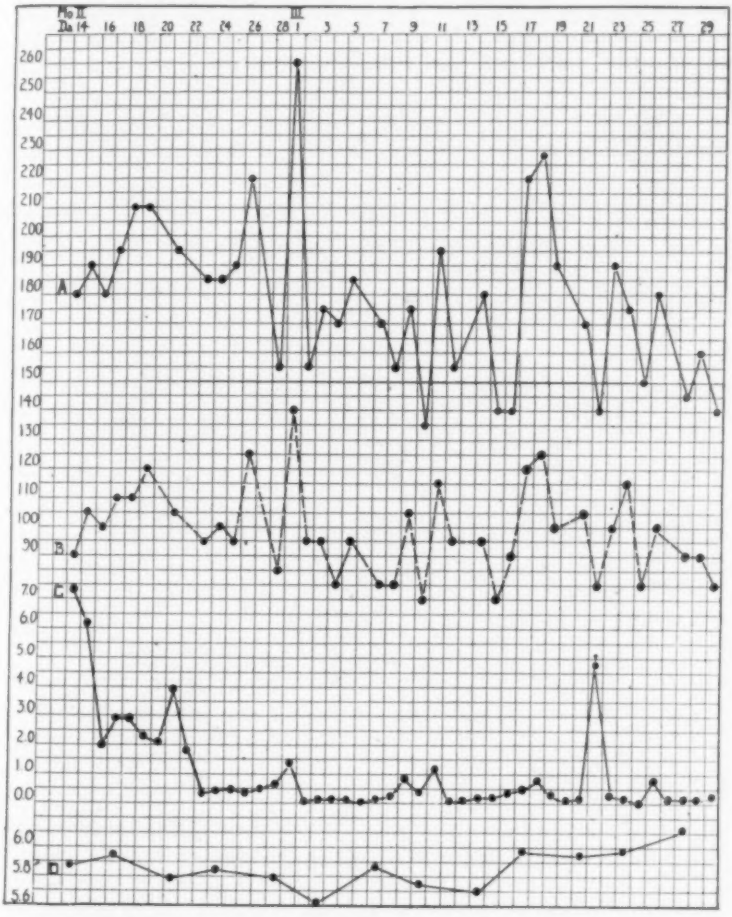

Chart 9 (Case 14).—This illustrates the effect of nervous influences. *A* represents systolic blood pressure; *B*, diastolic blood pressure; *C*, twenty-four hour urine chlorid in grams; *D*, plasma chlorid in grams per liter.

fall in salt to almost 3 gm. was accompanied by a rise of 22 mm. systolic pressure. The diastolic pressure was fairly constant.

This chart is almost similar to the previous two, except that it is somewhat more striking. There are four things that are especially

worthy of note. The first is the gradual rise in pressure, in spite of a low salt excretion, before the patient was sent home. The second is the sharp rise of 58 mm. systolic and 20 mm. diastolic pressure two days after leaving the hospital. At this time, the salt excretion was 0.5 gm. Such a rise was undoubtedly the result of conditions at home. The excretion on July 28 of over 13 gm. of salt with a pressure that fell to normal is especially noteworthy. Last but not least is the tendency for the systolic and especially the diastolic pressure to fall slightly during the very high salt feeding.

It is hard to believe from these experiences with high salt intake that the salt has much to do with the level of the blood pressure.

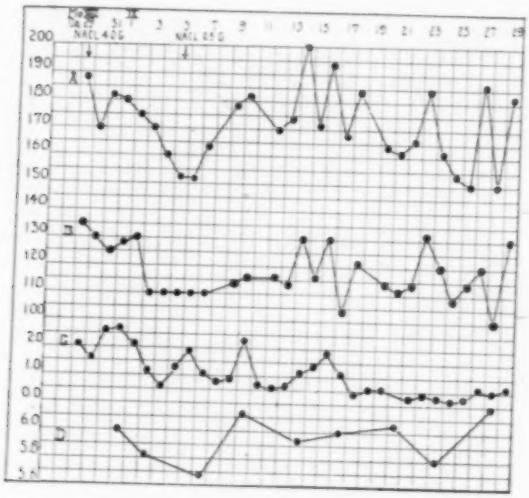

Chart 10 (Case 9).—The patient was on a 4 gm. salt intake diet up to September 5. From that date he was taking only 0.5 gm. *A* represents systolic blood pressure; *B*, diastolic blood pressure; *C*, twenty-four hour urine chlorid in grams; *D*, plasma chlorid in grams per liter.

Two charts are appended which illustrate various obvious difficulties in accepting the idea that low salt intake is effective in hypertension. Chart 9 demonstrates the extreme variability in pressures that, to say the least, is not prevented by the very low salt diet. Note particularly the sharp changes in pressure on March 1 and 17, with no corresponding changes in salt excretion. An increase of 105 mm. and 80 mm. systolic and 55 mm. and 30 mm. diastolic pressure in twenty-four hours is difficult to attribute to the changes that took place in the salt at those times. In Chart 10, note particularly the primary fall in pressure during the 4 gm. salt regimen and the paradoxical marked rise in

pressure following the decrease to an 0.5 gm. intake. One may point, by way of objection, to the rise in plasma chlorid with this rise in pressure. The former, however, is still within normal limits. Furthermore, we have previously demonstrated the lack of relation between the plasma chlorid and blood pressure. Lastly, this does not at all influence our main contention that the 0.5 gm. salt intake does not materially decrease the pressure.

CONCLUSION

The experiences detailed above, with the extremely low salt intake advocated for the treatment of hypertension, do not indicate any special advantage over the older less rigid restriction. The former regimen has certainly not fulfilled in our patients the conditions mentioned in the introduction. This very low salt diet is, furthermore, difficult to carry out at home, is monotonous and expensive. This paper also suggests that salt plays little part in vascular hypertension.

SPECIFIC TESTS IN THE DIAGNOSIS OF ALLERGY

W. W. DUKE, M.D.

KANSAS CITY, MO.

There are few subjects before the profession today more interesting and important than specific hypersensitiveness. The condition is common and afflicts perhaps 12 to 15 per cent. of adults.

Several sources of information are useful in the diagnosis of hypersensitiveness. From them, one can usually discover not only whether or not a given illness is fundamentally allergic in origin, but also what the specific allergen responsible for the illness may be. These sources of information are (1) family history; (2) personal history; (3) examination; (4) observation by the patient, and (5) specific tests (cutaneous, ophthalmic, nasal, subcutaneous, clinical, etc.)

Each source of information is important and, depending on the case, one may be more important than the others. For this reason, each will be discussed in some detail.

FAMILY HISTORY

Specific hypersensitiveness is one of the most consistently hereditary of diseases. In outspoken cases, a positive history of the condition in one or both parents can be elicited in almost 50 per cent. of cases. Cooke and Adkinson each report an antecedent history of allergy in 48 per cent. of cases studied. Each also found that, with a positive history in both parents, the disease appeared at an earlier age than when it obtained in one parent only. A positive family history, therefore, is very important confirmative evidence in the diagnosis of allergy.

PERSONAL HISTORY

A number of symptoms are characteristic of allergy. Worthy of especial mention are the ocular (edema of the conjunctivae, puffiness, redness, swelling and itching of the lids, and increased lacrimal secretion); the nasal (sneezing, pallor and swelling of the mucous membrane of the nose, associated with watery or clear mucous secretion); the pharyngeal (itching of the soft palate and pharynx, and cough); the bronchial (bronchial obstruction associated often with wheezing and the expectoration of clear mucoid sputum rich in easinophils—in lighter cases, cough and shortness of breath on exertion), and the cutaneous (urticaria, angioneurotic edema, eczema, erythema, pruritis). Much less characteristic are the gastro-intestinal symptoms (abdominal pain,

often following the ingestion of certain foods, and gastro-intestinal upset presenting a variety of symptoms); the bladder symptoms (frequent painful urination), and headache, nervousness, asthenia, hypotension and the like. The foregoing symptoms always suggest the possibility of allergy, especially when they occur in the absence of other apparent adequate cause for an illness, and when the family history is positive.

PHYSICAL EXAMINATION

The more important signs of allergy which can be found on physical examination are the ocular, the nasal, the bronchial and the cutaneous. The cutaneous symptoms can often be brought out by scratching the skin. This occasionally gives rise to the immediate appearance of typical wheals. Examination is also important in excluding sources other than allergy for a given complaint. For example, if, in a patient with a long history of frequent and painful urination, physical, cystoscopic, endoscopic and roentgen-ray examination, and uranalysis reveals nothing abnormal, bladder allergy must always be suspected, especially if the patient gives a history of hives, asthma or other characteristic symptoms of the condition, and if a history of such symptoms in the parents can be obtained.

OBSERVATIONS BY THE PATIENT

Practical observation by both physician and patient is important. It is often advisable, in an obscure case, to school the patient thoroughly in the mechanism of allergy so that his observations may be directed along useful channels. He should observe whether or not the origin or relief of symptoms bears any relationship to season, time of day, geographic situation, local environment; the proximity of animals or fowl, the eating of food, the use of cosmetics, wearing apparel, odors, habits, etc. Important information can often be gained through careful observation by the patient, which makes a correct diagnosis possible.

I may mention the history of a woman who was subject to asthma while in her own house but was relatively free of asthma in other localities. She gave a positive skin reaction to an extract of dust taken from her vacuum cleaner. She remembered, then, that her asthma, of four years' duration, dated from the purchase of new furnishings for her house, among which was a large rug. The rug was thoroughly cleaned with a vacuum cleaner, and saline solution was allowed to filter through it six times. The solution was then filtered through a stone filter, and injected intracutaneously. A marked local reaction and an attack of asthma immediately followed. Disposal of the rug resulted in an immediate cure. The patient was not sensitive to wool or other animal hair, nor to extracts similarly made from other articles about her house.

Symptoms which appear only in the spring, summer or fall, or bear a relationship to geographic situation are usually traceable to plant life

(usually to pollen, less often to emanations from the bloom, leaves or stalk). Symptoms which bear a relationship to local environment, such as house or work shop, are usually traceable to dust or some article or animal in the house. Among dentists, eczema or asthma is frequently traceable to sensitiveness to cocain, procain or apothesin. An undertaker whom we examined was sensitive to formaldehyd; a patient, subject to chronic asthma, worse in her own home than elsewhere, had a severe attack after the painting of her house and was proved sensitive to turpentine; another, subject for several years to nasal allergy, proved sensitive to orris root. She was relieved after discarding cosmetics, and especially after dispensing with a sachet which she kept in her dresser drawer. Occasionally, it seems impossible to discover the specific allergen responsible for house allergy, and one of our patients has had to give up his business on this account.

Symptoms which bear a relationship to stables are usually traceable to an animal, occasionally to emanations from vegetable matter, such as hay. Symptoms which bear a relationship to city or railroad cars are often traceable to smoke; to farms and country, often to plant life; to time of day, usually to an article with which habit brings the patient in contact. Night asthma is often due to house dust, wool or feathers. Asthma of any sort, whether of cardiorenal, emphysematous or allergical origin, is inclined to be worse at night.

Symptoms which follow the eating of certain meals are often traceable to an article of food; if the symptoms appear frequently, to a common article of food, and if rarely, it is an unusual article of diet.

Often the working out of an obscure case depends as much on detective work as on the persistence of the physician, and success can occasionally be attained only by visiting the patient's home or shop, and making careful observations.

SPECIFIC CLINICAL TESTS

Useful crude clinical tests can often be made by having a patient eat a suspected food, or inhale a suspected vapor or the odor of suspected perfume, or the emanations from fur, feathers, animals, etc., or by the application of suspected substances to the skin, etc. Such tests often make a correct diagnosis possible in the easiest sort of way. Frequently, however, this method of testing presents difficulties. In a person who is sensitive to several articles of food, such as milk, eggs, and certain vegetables, the greatest persistence in eating or in avoiding certain foods may fail utterly to give the diagnosis. This is especially true when reactions are delayed. In one patient with asthma who had been treated by several careful physicians, the primary sources of the disorder (which proved to be both milk and egg) were missed

entirely by clinical tests because the patient gave delayed reactions in each case and was sensitive to two common articles of diet. After the offending allergens were discovered through the use of cutaneous tests, the patient was able to obtain complete relief by their avoidance. The diagnosis was then proved by the fact that thereafter the patient could bring on a typical attack of asthma by the ingestion of a small amount of either milk or egg. The symptoms never appeared sooner, however, than thirty-six hours after either the intracutaneous injection or the ingestion of the offending substances.

SKIN TESTS

Two methods of making skin tests are used at the present time, the cutaneous or scratch method, advocated particularly by Walker, and the intracutaneous, advocated by Cook and others. Both have a sphere of usefulness. The intracutaneous, the more delicate method, gives a far greater number of positive reactions than the cutaneous, but has the disadvantage of giving a greater number of false positive reactions, or, rather, giving a greater number of positive reactions in patients who are not clinically sensitive. This is no great handicap, if the results are taken for what they are worth and what they actually indicate, and are used only in conjunction with information gained by history, physical examination and special tests. In this case, they are valuable, and rarely lead to serious error. The cutaneous reactions (or scratch tests) have their greatest sphere of usefulness in the testing of children and of patients sensitive to pollen and other air-carried allergens. Patients of these types respond readily, as a rule, to cutaneous tests. Scratch tests are useful also for testing patients sensitive to agents such as turpentine, benzol, and other substances which might prove irritating or harmful if injected intracutaneously. Cutaneous tests often fail utterly in older individuals and in patients whose symptoms appear to occur as a result of a general reaction, as in food cases. In these, intracutaneous tests often give marked and convincing reactions.

In our experience, both the cutaneous and the intracutaneous methods are useful, and neither should be used altogether to the exclusion of the other.

METHODS OF MAKING TESTS

Methods of making tests are described in some detail because, in this work, relatively simple and at the same time relatively accurate methods are almost essential if this sphere of knowledge is to be used broadly by the profession, as is also liberality in the interpretation of results obtained.

By Walker's cutaneous method, the foreign materials in dry powdered form are applied to scarified areas on the skin, and to this is added a drop of tenth normal sodium hydroxid solution. The appearance of a hive, with pseudopods surrounded by an irregular area of erythema, indicates a positive reaction.

Cook and his associates use standardized solutions in varying strengths and inject intracutaneously 0.01 c.c. The appearance of a hive, with pseudopods and erythema, indicates a positive reaction. Small reactions without pseudopods are disregarded. This method, while technically difficult, is very useful, especially in patients whose skin does not respond readily to cutaneous tests. The difficulty in technic does not lie in the injection of the solutions but in the preparation of solutions for testing. At the present time, it necessitates a physician's repeatedly making and standardizing several hundred stock solutions of his own. This can be handled practically only in well organized laboratories.

During the last year, I have used a method similar to Cook's, but in previous years, I used one which was much simpler in testing for sensitiveness to food proteins. It is not so accurate as Cook's, and is not adapted to testing for sensitiveness to pollen and other air-carried allergens because of the solution being too concentrated. It is useful for physicians who make tests on only a few patients a week.

SIMPLE PLATE METHOD

About 0.1 mg. of each of the suspected substances (in dry powdered form) to be used in the tests is placed on a large sterile plate. One-tenth mg. of a powdered protein can be guessed at crudely as the amount of powder which can be taken up easily on the end centimeter of a sterile Peerless round wooden applicator. To each protein, 0.1 c.c. of physiologic sodium chlorid solution (distilled water will not dissolve globulin) is added. The first solution to be used is stirred and drawn up in a tuberculin syringe provided with a small needle. Then 0.01 c.c. of the solution is injected intracutaneously. The syringe is washed carefully in each of three separate vessels containing sterile physiologic sodium chlorid solution. The syringe can then be used for injecting allergen No. 2, and so on, if the syringe is washed thoroughly, and if the vessels of salt solution are always used in the same rotation.

Fontaine has suggested the use of 0.1 mg. tablets of allergen instead of the powders as used above. This modification reduces the limit of error, and also is easier to carry out. For physicians who test out a number of patients daily (from five to ten), the use of stock solutions is much better and can be accomplished by dissolving 1 mg. powders or tablets in rubber stoppered phials containing from 1 to 3 c.c. of Coca's solution or sterile physiologic sodium chlorid solution to which has been added phenol 0.5 per cent. as a preservative.

The advantage of this method lies in the fact that allergens in the form of a powder keep potent indefinitely if dry (according to my

experience, more than six years), while solutions tend to deteriorate rapidly unless kept at icebox temperature. For this reason, potent allergens in the form of powders can be dispensed by commercial chemists and can be kept indefinitely, thus relieving the practitioner of the laborious process of repeatedly making and standardizing his own solutions.

That this method can be criticized as rather inaccurate is admitted. It is inaccurate, but no more so than any cutaneous (or scratch) method. Inaccuracy in the scratch method lies in the fact that the quantity of allergen absorbed by the skin is an unknown factor, as is also the strength of the solution formed after the mixing of powder and solution on the skin. Methods of testing cutaneously or intracutaneously are of necessity inaccurate in many cases. We often have no knowledge whatever of the substances with which we test our patients and to which they react.

I may mention the case of a physician who was subject to abdominal seizures which I suspected were allergic in origin and due to the occasional use of acetylsalicylic acid. On account of the physician's statement that he often took acetylsalicylic without ill effect, we tested him intracutaneously with five different brands. He gave negative reactions with four and an intensely positive reaction with one. Further than this, he was able to provoke an abdominal attack with the preparation to which he gave a positive cutaneous reaction, while the others caused no ill effect. He was evidently sensitive to some impurity contained in the one preparation. The impracticability of standardizing such an impurity for use in cutaneous testing is self-evident.

In citing this case, I do not wish to be taken as advocating inaccurate methods when accurate methods can be used. I simply advocate inaccurate tests rather than no tests at all.

One frequently wishes to test a patient with some substance for which he has no stock solution, such as a certain variety of straw, clover, newspaper, a dress, carpet, upholstery and dust. Suitable extracts of such substances can often be made by allowing them to stand several hours in a solution such as described by Wodehouse and Olmsted, or in Coca's solution, and filtering for the sake of sterility through a Berkefeld filter. It is usually impossible to standardize a solution of this sort since the offending element is an unknown quantity.

It is hardly necessary in a paper of this scope to describe in detail the methods of preparation of solutions of the different types, since this has been admirably done in a recent article by Coca and by Wodehouse and Olmstead. It may be well, however, to mention the fact that in making a preparation for cutaneous testing one should endeavor to obtain the suspected substance in relatively concentrated form. If an individual is thought sensitive to emanation from clover, the extract should be made of the whole, unbruised stem, leaf, or flower, the idea

being to get in solution a maximum quantity of the substance contained in the outer part of the plant. In the case of food hypersensitiveness, the inner portion of the article is likely to be as important as the outer, so that maceration before extraction is desirable. One must add here that efforts at purification of any extract are usually inadvisable. Purification would be the logical thing if one knew the particular constituent responsible for illness. When an individual is sensitive, however, to a substance such as grain, it is impossible to surmise at the outset what substance is primarily responsible, and in the process of purification the real offender might be lost.

While purification of an extract is, in general, inadvisable, the use of purified extracts often gives useful information in the case of common foods, such as eggs, milk or wheat; that is, foods which are used so frequently in cooking as to be difficult to avoid. In the case of egg, if a person is proved sensitive to either egg white or egg yolk protein alone, the offending substance can be removed mechanically, and the remaining portion of the egg can be used. Furthermore, cooked egg (coagulated protein) in this case may be tolerated. This information may enable a person to use cooked egg, cake, coffee in which egg is used in the clearing, etc., so that the avoidance of egg becomes no real hardship. In the case of ovomucoid, which is not coagulated by heat, it is necessary for the patient to avoid not only raw egg but cooked egg as well, in fact, occasionally, every food which contains even a trace of cooked egg. Likewise in the case of proved sensitiveness to lactalbumin, the milk may be rendered harmless by such a simple measure as boiling; while sensitiveness to casein may necessitate the discarding of milk altogether. Patients sensitive to certain raw foods are very often insensitive to the foods when they are thoroughly cooked. A knowledge of this may be a great convenience in choosing a diet.

Pollen allergens and some of the animal danders and other air-carried allergens should not be handled so promiscuously nor in the same concentration as food allergens. These allergens are, as a rule, stronger; they provoke more severe reactions, and they give convincing results when used in more dilute solution. Pollen extracts of a strength of 0.01 mg. of dry pollen to each cubic centimeter is usually concentrated enough to give marked reaction, in sensitive individuals. In group testing, usually 0.001 + mg. to the cubic centimeter of each individual pollen is adequate.

PRELIMINARY GROUP TESTS

The procedure of intracutaneous testing can be shortened and simplified somewhat through the use of preliminary group tests; that is, through the use of mixtures of from five to eight closely related

allergens. In the group tests, it is advisable to use less of each individual allergen than in the making of individual tests. I use no more of the mixture than of the individual solutions in the final tests.

Preliminary tests made in this way often enable one to say that a patient is sensitive to a certain mixture of vegetables, grains, animal dander, sea foods, etc. Further tests can then be made with each allergen contained in the mixture giving positive reactions, and frequently a great deal of time and trouble for the patient can be saved.

No hard and fast conclusions can be drawn from preliminary group tests. It is simply a useful means of getting a clue. One often finds that a group reaction comes out more strongly positive than tests with any individual member of the group, and vice versa. One should not let a negative group test interfere with his trying any individual constituent of a mixture should he suspect it as a cause of illness.

Cooke has very properly warned against the use of a large number of tests at one sitting. We have employed the method described above for more than two years, using usually more than 300 allergens at one sitting. We have had a few severe constitutional reactions, but have not had an alarming reaction. We have been very careful, however, with certain cases, especially pollen cases during the pollen season. The use of a large number of allergens to which a patient does not react should have little or no ill effect.

Before leaving this subject, one should again warn of the danger of violent constitutional reactions which occasionally follow intracutaneous injections. One should have epinephrin and atropin on hand ready for quick use, and should use it immediately and freely if coryza, asthma, generalized erythema or itching of the skin develops. Patients should not be allowed to leave the office sooner than one half to one hour after the tests are completed and should then be warned of the possibility of a reaction appearing even later.

ONE SYRINGE METHOD

It is rather impracticable for the profession generally to use a large number of syringes and needles in making intracutaneous tests; and it is unnecessary. In our work, we use one syringe and one needle. After making an injection, we wash it thoroughly in each of three vessels containing sterile salt solution. The first vessel dilutes the allergen greatly, the second more yet, and the third to such an extent that any trace which remains in the syringe is too dilute to interfere with the accuracy of subsequent tests. The third water is not contaminated sufficiently to interfere with the use of the same three solutions for further washing of the syringe; that is, if the three vessels are always used in the same rotation. If one wanted to be

more careful, he could do so by using four or five vessels of salt solution instead of three. This is unnecessary, however, if one is thorough in his washings. I frequently find one test intensely positive and the next negative, proving thus that the cleansing of the syringe must have been adequate.

INTERPRETATION OF CUTANEOUS TESTS

One's first impression of intracutaneous testing is likely to be one of disappointment. If he is so unfortunate as to be seriously misled by them, the first impression may be one of disgust. The fault lies more often, however, in the interpretation of results than in defects in the method itself.

In order to interpret correctly, it is necessary to bear in mind two facts: (1) that a strongly positive intracutaneous reaction with a given substance does not necessarily indicate that it is responsible for an illness, and (2) that a negative reaction with a given substance does not exclude it as a cause of illness. A positive reaction, excluding those which occur as a result of traumatizing a skin rendered unusually sensitive by allergy, indicates simply that the skin is sensitive to a given substance when given intracutaneously. It does not indicate that the patient is sensitive to the substance as encountered in natural ways. In other words, the patient, although actually sensitive, may tolerate the substance as encountered naturally, and in the dosage encountered naturally.

One patient subject to no apparent illness, except autumnal hay-fever, gave intensely positive intracutaneous reactions to each of about twenty spring and fall pollens; to several specimens of animal hair, and to several proteins extracted from fruits, vegetables and grains. He was ill, so far as one could judge, only in the fall, and could relieve himself by a change in geographic situation. He was evidently sensitive to many substances, but his tolerance was such that none except fall pollen as encountered in his mode of living made him ill.

A somewhat different type of case is that of a patient with active tuberculosis who was subject to asthma, regardless of season or geographic situation. She gave positive skin tests to wheat. Avoidance of wheat in the diet gave her no relief whatever, but avoidance of contact with flour (inhaled while making bread) gave her great relief, even when she ate wheat bread freely.

This finding might be explained in several ways. It is possible that the nasal mucous membrane was intolerant of wheat flour when inhaled, but was tolerant of the small amount reaching it through the blood stream after the ingestion of wheat. It may have been, on the other hand, that the flour was so changed by cooking or by digestion that the product to which she was actually sensitive was destroyed. It is well known that patients sensitive to lactalbumin (a protein of milk coagulable by heat) who are made ill by small amounts of raw milk can tolerate often almost unlimited quantities of boiled milk.

As regards the fact that patients proved sensitive to a given substance may give negative intracutaneous reactions, I believe, without compiling accurate statistics, that this condition is encountered more frequently in older individuals than in children; also, more frequently in individuals whose symptoms occur as a result of a general reaction than in individuals sensitive to air-carried allergens. A negative reaction is found more often in patients who have asthma, hives, or angioneurotic edema caused by ingestion of egg (general reaction) than in patients who have hay-fever or asthma caused by local contact of the respiratory mucous membrane with pollen or emanations from animal hair, etc.

In searching for an explanation of this fact, it might be mentioned that patients sensitive to a food can be sensitive to the food as it exists in a natural state or to some product elaborated during its digestion or putrifaction in the alimentary canal, or to some product formed by the parenteral alteration of some of its products after absorption. A patient with egg urticaria may be insensitive to egg but sensitive to a product formed from egg after many catabolic and anabolic processes. I observed a patient with egg asthma who gave a very slight skin reaction, but who was clinically so sensitive to ovomucoid that three drops of a solution of whole fresh egg made by diluting one drop of fresh mixed egg with 200 c.c. of water was sufficient to cause severe asthma, if taken by mouth. The same result appeared after the subcutaneous injection of 0.0001 mg. of whole egg. The reactions produced in either way did not appear sooner than thirty-six hours after the treatment with egg.

The mere fact that the nasal mucous membrane or gastro-intestinal mucous membrane is sensitive to and reacts to a given substance does not necessarily mean that the skin is sensitive and should react positively. It is simply good fortune that the skin does react positively so often.

Given the facts that a negative skin reaction does not exclude a given substance as a cause of illness and that a positive reaction, although indicating sensitiveness to the substance, does not indicate that it is a cause of illness, the following general rules are of value in interpreting results:

1. Occasionally, the skin reacts to one substance only. When this is the case, the real offender, as a rule, is discovered.

2. The skin usually reacts to several substances and often to several groups of substances. When this is the case, the larger wheals usually indicate the real offenders. This is not invariably so. A patient may react markedly to vegetables and slightly to grains and be made actually ill by a grain only. The fact that extracts prepared for cutaneous

testing contain a large variety of chemical bodies may account for this circumstance. The allergen responsible for an illness may be the largest constituent of the mixture or the smallest constituent. If the offending allergen is the smallest constituent, the skin reaction may be less marked than that produced by mixture containing a less offensive allergen in larger amounts. It may be mentioned again that marked skin sensitiveness does not necessarily indicate marked sensitiveness to the substance as encountered naturally.

A woman who had been subject for months to almost daily spells of abdominal pain and vomiting, was emaciated and seemed unable to tolerate any type of diet which was chosen for her. She gave positive intracutaneous reactions to almost every type of food, although to some much stronger than others. After many combinations of food in the diet had been tested without benefit, she was put on a diet confined to meats and fruits. She was absolutely free of symptoms while on this diet and gained, in a short time, over 40 pounds (18 kg.) in weight. Many attempts were made to add to the diet, but without success. The least digression caused immediate recurrence of vomiting and pain. Milk and eggs, which did not give strong skin reactions, were not tolerated even when taken in small amounts.

Although the foregoing facts may be disturbing to those enthusiastic over the possibilities offered by cutaneous tests, they are less disturbing than error; and if one bears in mind the fact that positive skin tests indicate sensitiveness only to an allergen as applied in the test and not necessarily sensitiveness to an allergen as it is encountered in nature, one can often gain many useful clues without being seriously misled. A clue gained from a skin test should never be looked on as diagnostic but should be used as a clue only. The diagnosis should be verified by and based on history and examination, and on other tests to be mentioned subsequently.

OPHTHALMIC AND NASAL TESTS

The ophthalmic and nasal tests are especially useful in picking out pollens or other air-carried substances responsible for hay-fever and asthma. These tests should be made after the results of intracutaneous testing have been observed. The ophthalmic test is made by spraying pollen solution (1:1,000 extract from dry pollen) into the conjunctival sac. A positive reaction is indicated by redness of the conjunctiva and increased lacrimal secretion which persists for more than five minutes. Momentary redness cannot be considered positive. The effect of a positive reaction may be immediately relieved by instilling a drop of epinephrin (1:1,000 solution) in the conjunctival sac.

The nasal test is made by spraying a pollen solution (1:1,000 solution) into the nose. A positive reaction is indicated by sneezing, swelling of the nasal mucous membrane, and watery or clear mucous

secretion which persists for several minutes or more. The ill-effect of this reaction can also be relieved by the local use of epinephrin.

These tests are especially useful in pollen cases, and with their aid one can often pick out from a group of pollens which give positive cutaneous tests the one particular pollen responsible for clinical symptoms.

In a patient who gave positive intracutaneous tests to almost every fall pollen which was used in testing, *Artemesiaefolia* was the only one of the group which caused a positive ophthalmic reaction. She was treated with *Artemesiaefolia* extract for several months before the hay-fever season began and was apparently rendered so tolerant of this pollen that, although she continued to give a positive skin reaction to it, she had no symptoms of hay-fever during the entire season. The inference might be drawn in this case that, although she was sensitive to many pollens before treatment, tolerance for all except *Artemesiaefolia* was such that she could stand without difficulty the amount encountered naturally in her ordinary habits of life.

Ophthalmic and nasal testing is limited in usefulness because relatively few tests can be made on a patient in one day. A positive reaction prevents further use of the eye for testing for a day or two. A negative reaction does not interfere with further testing, and often if one suspects one of a group of, say, six different pollens, the entire six may be tried, provided the ones which give the positive reactions are used last.

Patients who are clinically sensitive to a pollen usually react positively to a 1 : 1,000 solution. Occasionally, they do not. It is possible that stronger solutions might be used in an effort to provoke a positive reaction. We have not studied this point, since a majority of patients do react to the solution as described. It is not out of line with our knowledge of facts that patients who fail to react to a 1 : 1,000 solution of a given pollen extract can be actually clinically sensitive to the pollen as encountered in nature. It must be borne in mind that during the pollen season, the conjunctivae encounter pollen dry and untreated. It is not difficult to conceive that the exposed tissues may react to dry untreated pollen even though insensitive to pollen in high dilution.

Nasal tests are also useful for testing in a simple way for sensitiveness to animal hair, feathers, or emanations from vegetable matter, etc. The test can often be made by having the patient inhale from the substance to be tested and noting whether or not it causes sneezing or other symptoms resembling hay-fever. I obtained a very convincing reaction in a carpenter who was troubled with nasal and bronchial allergy while in his work shop. He had a violent attack of sneezing when asked to inhale from a bag of birchwood shavings. The inhalation from shavings of seven other woods caused no symptoms whatever. It is often possible to get reactions of this sort with feathers or furs, or sometimes with solutions such as perfume, cedar oil, turpentine, smoke and like substances.

One must carefully discriminate between patients who are actually specifically hypersensitive to a substance of this kind, and those who have a nasal allergy due to other causes and who give a positive nasal reaction due to the nonspecific irritating effects of the substance used in the test. Patients with pollen asthma will frequently be made to sneeze or to suffer an aggravation of their symptoms if they inhale perfume, smoke or dust. The inhalation of these substances, however, may have no untoward effect on them except during the pollen season. In other words, though made worse by their inhalation, these patients may not be actually specifically hypersensitive to them.

SUBCUTANEOUS TESTS

Subcutaneous tests have their greatest sphere of usefulness in confirming a given diagnosis. If one suspects artemesiaefolia as a cause of hay-fever, and can inject a small quantity of *Artemesiaefolia* pollen extract subcutaneously during a well period and reproduce the symptoms of hay-fever, he should feel convinced that *Artemesiaefolia* is the probable cause of illness. Similarly, if one believes sensitiveness to milk is responsible for abdominal pain or bladder disorder, and can reproduce these symptoms during a well period by subcutaneous injection of milk, he should feel that he is on the right track.

In order to prevent severe constitutional reactions, subcutaneous tests should be used with great care, and only minute amounts should be injected. If one suspects lactalbumin as a cause of asthma, not more than 0.0001 c.c. of lactalbumin should be given subcutaneously as an initial dose. If this should fail to produce asthma, a larger dose might be administered. The ill-effect of a reaction can be combated almost immediately, as a rule, by the subcutaneous injection of 0.5 c.c. of epinephrin (1:1,000 solution). If there are no signs of relief within two or three minutes, 0.25 c.c. doses can be repeated at from two to five minute intervals until relief is obtained.

The sensitiveness of some patients to foreign materials is extraordinary, and anyone dealing with this subject should bear this fact in mind. One person with asthma whom I observed was so sensitive to wood smoke that the application of a drop of Wright's concentrated wood smoke to a scratch on the skin produced not only a wheal which reached from shoulder to elbow, but also asthma, coryza, erythema of the skin and a general reaction, which necessitated the hasty use of several doses of epinephrin.

DIAGNOSIS

In a relatively large proportion of cases of allergy, the diagnosis is apparent, and can be made by history and physical examination (pollen hay-fever and asthma, for example). In obscure cases, in which the

condition is not self-evident, the diagnosis should not be based on one series of facts but on several. If allergy is the suspected cause of an obscure illness, a positive family history or a history of other typically allergic symptoms in the same individual is important confirmative evidence. Cutaneous tests, subcutaneous tests and other specific tests are of additional value.

The diagnosis should rarely be considered conclusive, however, until the allergen responsible for the illness is found and removed, with relief to the patient, and finally confirmed further, if possible, by the reproduction of the illness during a well period by the patient's being again brought in contact with the suspected substance. These criteria are important. A great many secondary factors aggravate allergic symptoms in sensitive individuals and lead to error in diagnosis. Patients with pollen asthma are usually made worse by several other agents which have no untoward effect on them except in the pollen season. Patients with gastric allergy due to hypersensitiveness to egg will almost invariably be made worse by rough foods, such as popcorn or nuts; by irritating foods, such as paprika or mustard, or by foods which stimulate the secretory activities of the gastric mucous membrane, such as alcohol, salt or sweets, so long as the gastric mucous membrane is in a reactive state due to the ingestion of egg. If egg is removed from the diet, these foods may cause no ill effect whatever.

Secondary factors often mislead both patient and physician, and cause one to suspect them rather than the primary factor as the cause of illness. Infection augments the symptoms of nasal and bronchial allergy. Patients with mild bronchial allergy (not bacterial in origin) are usually much worse during and after an attack of bronchitis. The organism responsible for the bronchitis might easily be suspected as the primary cause of the disorder; but when the allergen responsible for the condition is found and removed, further attacks of bronchitis amount to nothing more than slight cough of short duration.

Functional and organic diseases, as well as infectious diseases, can modify the symptoms of allergy and mislead a physician, as can reflexes also. Patients with asthma may be made either better or worse by eating a meal; by a movement of the bowels, taking an emetic; by changes in barometric pressure, temperature, or dryness of the atmosphere, or even by pressure or change of pressure in the nasal sinuses. These facts, while relatively simple to read, may be most misleading unless one is strict in establishing his criteria, and bases his final conclusion, not on one line of evidence, but on every line which is at his disposal.

SUMMARY AND CONCLUSIONS

Specific hypersensitiveness may be suspected in any person who has in his family or personal history, or who on physical examination

shows, certain rather typical manifestations of the condition: ocular, nasal, pharyngeal, bronchial or cutaneous symptoms. It may be suspected in patients who show certain less characteristic symptoms, if no other adequate cause for the disorder is found on examination: the gastro-intestinal, and bladder symptoms; headache; nervousness; asthenia; hypotension, etc. The foregoing symptoms suggest the possibility of allergy, especially when they occur in the absence of other adequate cause for illness, and when the family or personal history is positive.

In searching for the source of allergy, or rather for the specific allergen primarily responsible for an illness, careful observation by the patient is helpful and often makes complete study and a correct diagnosis possible.

Specific tests are often useful in gaining a clue as to the source of allergy. The cutaneous tests are useful in young persons or in persons sensitive to air-carried allergens. The intracutaneous are more useful in the less sensitive persons; i. e., older patients, those sensitive to foods, and those whose symptoms occur as part of a general reaction. Intracutaneous tests often result in positive reactions in patients who are not sensitive to the allergen as encountered in nature, and, vice versa, persons who are sensitive to certain allergens as encountered naturally do not always give positive intracutaneous reactions. For this reason, care should be used in the interpretation of skin tests, and a diagnosis should not be based on the results of these tests alone. These results should be used as a clue only and should be verified by other special tests, such as the nasal and ocular tests, or subcutaneous or clinical tests.

Many secondary factors modify the symptoms of allergy, such as infectious disease, functional or organic disease, reflexes, agents which irritate or stimulate either mechanically, chemically or otherwise, so that a diagnosis should be based, if possible, not only on the history of a case and physical examination but also on the apparent finding of the specific allergens responsible for an illness, on removal of the allergen with relief of symptoms, and, finally, on reproduction of symptoms during a well period by bringing the patient again in contact with the suspected substance. Few mistakes in diagnosis will be made when these procedures can be carried out fully, and conclusions can be based on adequate data.